Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):251-259
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Artículo especial

Costes frente a beneficios de los suplementos nutricionales orales

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Resumen

La economía de la salud pretende asignar unos recursos que son, por definición, escasos y que, a su vez, pueden ser invertidos para otros usos. El análisis de costes en salud pretende comparar los pro y los contras de diversas opciones entre las que se puede elegir, para obtener los mayores beneficios con menores costes.

La legislación actual sobre prescripción de nutrición enteral recoge definiciones confusas acerca de la vía de administración y los requerimientos en la nutrición enteral domiciliaria, no existiendo una normativa específica que recoja la prescripción de suplementos orales (SO).

Desde el año 2000 a 2007, el consumo de nutrición enteral domiciliaria en Andalucía aumentó notablemente, multiplicándose los costes generados por 37. Aunque el número de personas que consumieron diariamente suplementos fue superior al de las dietas por sonda (DS) durante todos los años evaluados, los costes derivados de los SO superaron a los de las DS a partir del año 2005, debido a la combinación de dos factores: incremento progresivo del número de personas a las que se les prescribieron suplementos y, por otro lado, por la incorporación de formulaciones específicas más caras. El empleo de suplementos orales parece ser coste/efectivo en pacientes quirúrgicos hospitalizados (en el pre y post operatorio) y, posiblemente, en ancianos malnutridos hospitalizados, especialmente tras realización de cribado de desnutrición. Aunque podrían ser eficaces, en otras circunstancias, como en pacientes ambulatorios, son necesarios más trabajos con metodología adecuada, para poder realizar decisiones clínicas basadas en la evidencia y en los análisis de costes.

(*Nutr Hosp*. 2009;24:251-259)

Palabras clave: *Nutrición enteral. Costes. Suplementos orales. Diabetes. Cáncer.*

COSTS VERSUS BENEFITS OF ORAL NUTRITIONAL SUPPLEMENTS

Abstract

Health economics pretends to assign resources that are short in essence and that may be used for other purposes. Health costs analysis pretends to compare the pros and cons of several options among which an election can be made in order to obtain greater benefits with lower costs.

The current legislation on prescription of enteral nutrition entails confusing definitions about the administration route and the requirements of home-based enteral nutrition, without a specific regulation comprising the prescription of oral supplements (OS).

From the year 2000 to 2007, the consumption of home-based enteral nutrition in Andalusia increased considerably; the costs generated being multiplied by 37. Although the number of persons that daily consumed supplements was higher than the number of diets through nasogastric tube (DT) during the years evaluated, the costs derived from OS surpassed those of DT from the year 2005 due to the combination of two factors: a progressive increase in the number of persons to whom supplements were prescribed, and on the other hand the incorporation of more expensive specific formulations. The use of oral supplements seems to be cost/effective in hospitalized surgical patients (during the pre- and post-surgical period) and possibly in hospitalized malnourished elderly, especially after performing a hyponutrition screening. Although they may be effective, under other circumstances, such as ambulatory patients, studies with an adequate methodology are necessary in order to adopt clinical decisions based on evidence and cost analysis.

(*Nutr Hosp*. 2009;24:251-259)

Key words: *Enteral nutrition. Costs. Oral nutritional supplements. Diabetes. Cancer.*

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Recibido: 8-XI-2008.
Aceptado: 4-I-2009.

Economía de la salud y principios de bioética

La *economía de la salud* es una disciplina relativamente nueva que pretende asignar unos recursos que son, por definición, escasos y que a su vez pueden ser invertidos para otros usos (sanitarios o no). Es importante recordar que la sanidad pública (que cubre prácticamente a toda la población en España) se financia a partir de los presupuestos generales del Estado y que existen previsiones de crecimiento continuo del gasto sanitario en los próximos años (desde el 6% del PIB actual al 8,42% en el año 2050) motivado por múltiples factores, entre los que destaca el incremento de la población anciana, que demanda mayores recursos sanitarios. El *análisis de costes en salud,* pretende comparar los pro y los contras de diversas opciones entre las que se puede elegir, no para gastar menos, si no para "gastar mejor", o dicho de otra forma, para obtener los mayores beneficios con menores costos.

La economía de la salud, como ciencia, trata de ofrecer el mayor grado de bienestar posible a partir de los recursos disponibles y éste es un objetivo ético, por cuanto se infiere que es ético ser eficiente. En este sentido los profesionales de la salud desempeñamos un papel importante ya que, a la vez que debemos lograr que los pacientes reciban una atención adecuada, con nuestras actuaciones estamos asignando recursos sanitarios. En 1979 Beauchamp y Childress propusieron los principios básicos de la *bioética*[1]. El *principio de beneficencia* establece que el profesional de la salud debe siempre procurar el bien de sus pacientes. Íntimamente asociado al principio de beneficencia está el principio de *no maleficencia,* que establece la necesidad de no hacer daño y expresa la prudencia en el ejercicio profesional de modo que no se perjudique al paciente con tratamientos dudosos o innecesarios. En este sentido el profesional no debe incitar el consumo de servicios de salud innecesarios o particularmente costosos en la búsqueda de su propio interés; el único interés que debe buscar el profesional es el beneficio del paciente. La formación continuada del profesional le ayudará a saber ofrecer a sus pacientes un tratamiento de la máxima calidad. Por tanto, cuanto más sólidos y profundos sean los conocimientos de la rama médica que ejerce y mayor su destreza para ponerla en función, más fácil le será actuar competentemente sobre bases más firmes. En este sentido, la Medicina Basada en la Evidencia (o en las pruebas)[2], entendida como un proceso sistemático de búsqueda, evaluación y uso de los hallazgos de la investigación biomédica, está mejorando la toma de decisiones en la práctica clínica nutricional repercutiendo en la asistencia de los pacientes y en la prevención de enfermedades. El *principio de autonomía,* proclama que se debe contar con la opinión del paciente a la hora de tomar decisiones. El paciente emitirá su opinión en base a sus creencias personales y a la información que reciba del profesional, por lo que se involucran el consentimiento informado y el deber de informar verazmente. El principio de autonomía limita el principio de beneficencia en el sentido de que el profesional debe contar con el beneplácito del paciente para su realización. Los límites a este principio le vienen fundamentalmente del principio de justicia del que hablaremos posteriormente, ya que, el bien común hace necesario poner límites a la libertad de elección de los pacientes. En el campo de la nutrición clínica, este principio puede ser muy importante a la hora de tomar ciertas decisiones como la indicación de nutrición enteral por sonda (nasogástricas o de gastrostomías) en oposición a la suplementación oral. El cuarto principio es el de *justicia,* según el cual una actuación no puede considerarse ética si no resulta equitativa, es decir, si no está disponible para todos aquellos que lo necesiten. Este principio vela por la imparcialidad en la distribución de los beneficios y los riesgos. Según Diego Gracia[3], los principios de no maleficencia y de justicia serían jerárquicamente superiores a los de autonomía y de beneficencia, pues se definen como criterios universales, ya que obligan aun en contra de la voluntad de las personas. No estamos obligados a hacer el bien a otro en contra de su voluntad, pero sí a no hacerle mal.

En muchas ocasiones, se producen conflictos éticos en la toma de decisiones sanitarias en función de los intereses de los actores que intervienen (gestores sanitarios, profesionales de la salud y pacientes o cuidadores) y del modelo teórico ético en que se sustentan las actuaciones (como el modelo liberal-radical, donde se defiende la libertad como un valor único y absoluto; el modelo utilitarista, donde el fin justifica los medios y estaría basado esencialmente en la relación coste-beneficio, el modelo sociobiológico o el modelo personalista, donde la persona es el valor supremo y no puede ser usada como objeto).

Estudios de costes en salud

El prototipo de análisis económico utilizado de forma más frecuente para la desnutrición es la aproximación al "coste por enfermedad"[4-5] que describe el coste de una enfermedad para la sociedad e incluye los conceptos de costes directos, indirectos y psicológicos (intangibles).

Los *costes directos* abarcan los gastos de hospitalización (en centros de agudos y de residencias geriátricas u hospitales de larga estancia), consultas externas, asistencia a domicilio, medicamentos, nutrición artificial y otras terapias. En general, tienden a ser los costes más fáciles de registrar y, por tanto, son los que se recogen en la mayoría de los estudios. A pesar de ello, son muy escasos los artículos que incluyen una evaluación económica en relación a la nutrición clínica y, aún menos, los que valoran estos aspectos con el uso de suplementos orales.

Los *costes indirectos* comprenden las pérdidas de productividad causadas por enfermedades a corto plazo, jubilación anticipada y muerte precoz antes de la

Tabla I
Tipos de análisis económicos

	Costes	*Resultados*
Minimización de costes	Monetario	Efectividad
Coste-efectividad	Monetario	Unidad clínica
Coste-utilidad	Monetario	QALYs
Coste-beneficio	Monetario	Monetario

jubilación. Debido a la dificultad para asignar valoraciones monetarias a esos parámetros, prácticamente no existen estudios que incluyan estos costes en nutrición clínica. Además muchos pacientes con desnutrición crónica, que requieren nutrición artificial domiciliaria o ambulatoria, son ancianos o con enfermedades graves por lo que tienen menos posibilidades de seguir en activo.

Los *costes psicológicos o intangibles* suelen despreciarse porque es difícil asignar costes a factores tales como el dolor o cambios drásticos en el estilo de vida, que afectan a la calidad de ésta.

A la hora de elegir entre distintas opciones terapéuticas en sanidad y lógicamente en nutrición clínica, la economía de la salud emplea diferentes opciones de evaluación económica[6-7] (tabla I):

Estudios de *minimización de costes:* Se usan cuando las alternativas que se comparan tienen el mismo resultado y la misma eficacia. Por ejemplo, si se demostrara que el uso de nutrición enteral por sonda vs suplementos orales son iguales de eficaces en revertir la malnutrición (y asumiendo que los resultados clínicos —morbimortalidad— son similares) lógicamente se debería usar la opción que fuera más barata. La alternativa de menor costo es la más eficiente. No obstante, para que se puedan usar los estudios de minimización de costes, se debe *demostrar* claramente que las alternativas tienen la misma eficacia y no sólo *asumirlo,* como se hace frecuentemente.

Estudios de *coste-efectividad*. Se usan cuando las alternativas que se comparan tienen el mismo resultado pero no tienen la misma eficacia, por lo que se debe medir el coste de alcanzar cada unidad sanitaria con cada una de las alternativas. Por ejemplo, nos puede interesar conocer si el uso de suplementos preoperatorios desciende las complicaciones postoperatorias en relación al tratamiento convencional (dieta oral únicamente). Los costes se miden en euros, dólares o la moneda que sea, y la efectividad en unidades naturales como vidas salvadas, años de vida salvados, complicaciones evitadas o días de estancia ahorrados. El resultado de estos estudios se expresa en un cociente de coste/efectividad. La estrategia más coste efectiva será la que consiga mejores resultados por el mismo o menos dinero. Un tipo especial de estudio de coste-efectividad es el *coste-utilidad*. Se usan cuando las alternativas que se comparan no tienen el mismo resultado ni la misma eficacia, o cuando una de las dimensiones importantes a tener en cuenta es la calidad de vida. Salvo excepciones, existen pocos trabajos que evalúen el coste-utilidad del uso de suplementos orales. Existe la dificultad añadida de asignar un valor monetario a la calidad de vida. Se suelen expresar como Años de Vida ganados Ajustados por Calidad (AVACs o QALYs). Es el método generalmente empleado por el National Institute for Health and Clinical Excellence del Reino Unido (NICE), para elaborar sus guías de práctica clínica. El resultado de estos estudios se expresa como un cociente coste/utilidad.

Estudios de *coste-beneficio:* Estos estudios relacionan los costes de un programa sanitario o un tratamiento con los resultados del mismo, ambos expresados en términos monetarios. En el caso de la Nutrición Clínica es difícil asignar costes monetarios a intervenciones cuyos beneficios se miden en calidad de vida o en mejoras funcionales (como son la mayoría de los estudios evaluados).

Los costes directos de la desnutrición

En España existen algunos trabajos que evalúan aspectos parciales de los costes asociados a la desnutrición, especialmente en pacientes hospitalizados. El grupo de Pérez de la Cruz[8] comunicaron que los pacientes desnutridos consumían un 68% más de recursos económicos que los normonutridos, debido a mayores estancias hospitalarias y consumo de fármacos y de soporte nutricional. Nuestro grupo[9] también comprobó que las personas desnutridas (según Valoración Subjetiva Global) tenían mayor número de complicaciones, estancias, costes y mortalidad que las personas normonutridas a pesar de ingresar por diagnósticos similares. El grupo de De Luis[10] publicó los costes directos de la nutrición enteral en un hospital terciario durante los años 1999 a 2001 (consignando únicamente el gasto correspondiente a las nutrilíneas, las fórmulas nutricionales y las sondas) correspondiendo un coste medio de 598,4 euros por paciente y de 36 euros por día. El mismo grupo[11] analizó los costes en 102 pacientes con nutrición enteral domiciliaria administrada por vía oral en el 79% de los casos, por sonda nasogástrica en el 15% y por ostomías en el 6%. El coste medio global por tratamiento completo y por paciente fue de 1.800 euros (18 euros diarios), siendo la mayoría del mismo derivado de la prescripción de preparados nutricionales (dada la baja casuística de pacientes con sonda). En el análisis económico no se incluyeron los costes por consultas, hospitalizaciones etc. Castillo y cols.[12] evaluaron el coste de la nutrición enteral domiciliaria en relación a las diferentes vías de acceso, demostrándose que, a pesar de que las gastrostomías suponen un mayor coste inicial, posteriormente sus ventajas económicas pueden ser superiores a las de otras vías. Castaño y cols.[13] publicaron un estudio sobre la prescripción de la nutrición enteral domiciliaria (a partir del análisis de las recetas públicas consumidas en la comunidad de Madrid en los años 1998 a 2001) y

observaron un incremento de la prescripción de envases y, especialmente notable de los costes asociados, debido principalmente a la incorporación de formulaciones de mayor importe y menos "estándar".

En el Reino Unido, se ha estimado que en el año 2003 (población 58.789.194 habitantes) la asistencia a las personas desnutridas generó unos costes directos para el sistema sanitario de aproximadamente 7,3 billones de libras[7]. Estas cifras fueron calculadas mediante modelos teóricos en los que se aplicaban valores de prevalencia de desnutrición (tanto en pacientes ambulatorios como hospitalizados) y asignando un valor económico al incremento de costes hospitalarios (por aumento de estancias); también se tuvieron en cuenta los costes de la nutrición enteral domiciliaria y las visitas ambulatorias a los médicos (de primaria y hospital). De los costes estimados, más del 50% correspondió a la hospitalización de personas desnutridas (fig. 1). Sin embargo, el coste generado por el tratamiento de la malnutrición en sí, mediante nutrición artificial, sólo supuso el 2% del total. Además, la mayoría de los costes totales (casi 5 billones de libras) fueron generados por la atención a personas ancianas (más de 65 años). De los datos aportados, es importante señalar que el 72% de los costes calculados fueron "exceso de costes", achacables directamente a la desnutrición. Estos costes están claramente estimados a la baja ya que utilizan datos de prevalencia de desnutrición moderados y, además, no incluyen costes indirectos. Hasta la fecha no existen datos similares publicados en España.

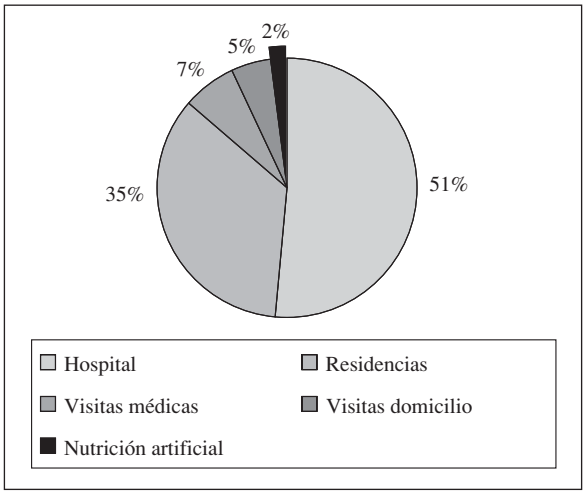

Fig. 1.—Distribución en porcentaje de los costes derivados de la atención a las personas con desnutrición en el Reino Unido (2003).

Situación legal de la prescripción de los suplementos en España

Tal como se recoge en el V foro de debate SENPE[14], sobre problemática de la nutrición artificial domiciliaria y ambulatoria, la legislación actual[15-16] sobre prescripción de nutrición enteral recoge definiciones confusas acerca de la vía de administración y los requerimientos en la nutrición enteral domiciliaria (NED).

Así, la normativa recoge que la "nutrición enteral será administrada principalmente por sonda y, ocasionalmente, por vía oral" y en la definición de fórmulas enterales para NED que "son una mezcla definida de macro y micronutrientes para su uso como única fuente nutricional, fabricadas para uso a través de sondas de alimentación y excepcionalmente por vía oral, con presentaciones líquidas o en polvo y que su proceso de fabricación debe ser diferente de la deshidratación directa o trituración de alimentos, o mezcla de alimentos de consumo ordinario, simple o elaborada".

Esta normativa crea confusión y fuerza la conversión de los suplementos orales en fórmulas completas (aunque, en la práctica, se presenten en envases pequeños, generalmente menores a 250 ml) y excluye a los productos de textura modificada vía oral, siendo necesario el empleo de la sonda.

Esta legislación teóricamente impediría, si se cumple la ley de forma estricta, el que un paciente con enfermedad neurológica progresiva pueda prevenir o tratar la desnutrición con aporte de NED por vía oral como paso previo a la sonda de alimentación definitiva. Por otro lado, sólo se considera NED a la administración de fórmula por sonda y que cubra más del 75% de los requerimientos.

Por tanto, la normativa no contempla la prescripción de suplementos orales con criterios clínicos, ni la atención específica a la disfagia. No obstante, para compensar, en el RD 1.030/2006, se recoge que "en el caso de pacientes con disfagia neurológica o excepcionalmente motora, pero que sufren aspiración o riesgo de aspiración para alimentos líquidos se les pueden indicar módulos espesantes" (también con requisito previo de visado de recetas).

La exclusión para nutrición enteral vía oral de la disfagia neuromotora tiene una importante repercusión socio-sanitaria ya que discrimina al mayor, especialmente al más frágil.

El marco legal se aleja, en la actualidad, claramente de la realidad ya que, como se recoge en el último registro que publica el grupo NADYA (del año 2006)[17], la mayoría de las prescripciones de NED se realiza por vía oral, siendo la enfermedad de base más frecuente la patología neurológica 42% (teóricamente no deberían beneficiarse muchos de ellos de esta prescripción), seguida del cáncer 28%. Es posible que la aplicación estricta de la legislación en los próximos años favorezca una reducción de la prescripción de NED en enfermedades neurológicas por vía oral.

Por otro lado, la normativa deja algunas ausencias notables en la lista de enfermedades aprobadas (como la caquexia cardíaca y respiratoria, la disfagia aislada, la insuficiencia renal crónica del adulto, la anorexia nerviosa o la rehabilitación tras enfermedad catabólica) que excluyen el criterio del facultativo y limitan la eficacia de su intervención.

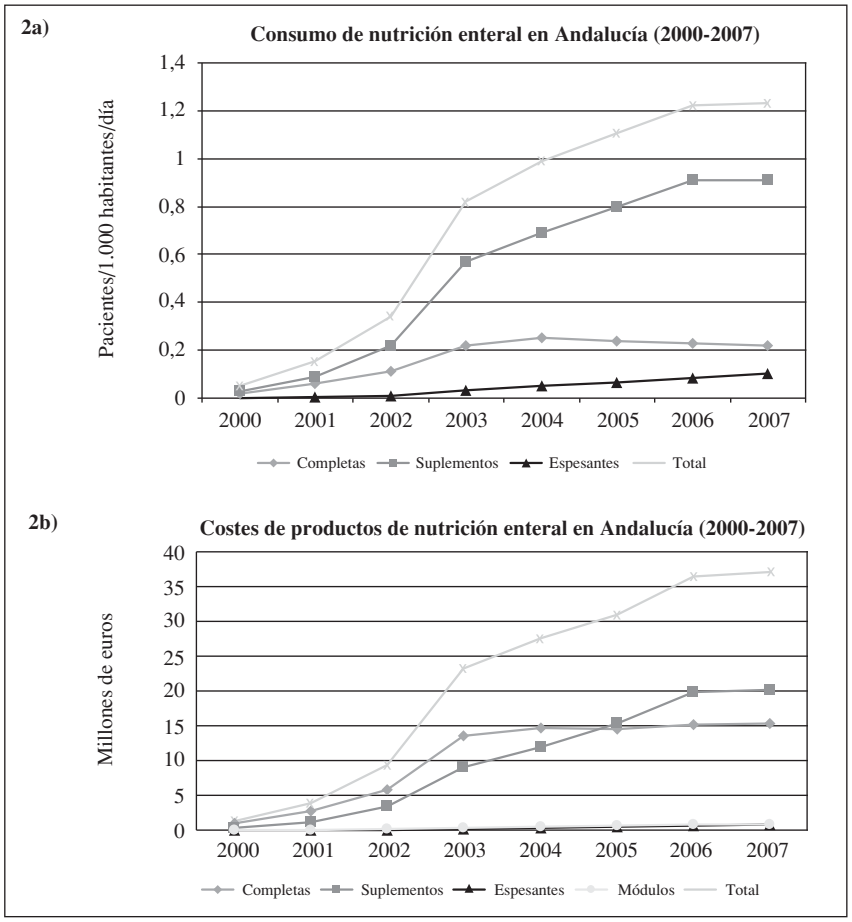

Fig. 2.—Evolución del consumo y costes de nutrición enteral domiciliaria en Andalucía (años 2000 a 2007).

En la legislación se deja entrever un difícil equilibrio entre los deseos de la administración (que debe velar por una racionalidad en la distribución de recursos y, por tanto, pretende limitar el empleo de una tecnología con un impacto económico apreciable en indicaciones de eficacia incierta y evitar abusos) y la de los profesionales (que intentan ofrecer al paciente concreto los mejores recursos disponibles para mejorar su estado nutricional, calidad de vida e, incluso en ciertas ocasiones, mejorar el pronóstico de la enfermedad de base)[18]. La demostración de una reducción de costes sanitarios asociada a la prescripción de suplementos orales sería, por tanto, un argumento más sólido para encontrar puntos de acuerdo con la administración.

La situación en otros países europeos es muy variable, dependiendo de la legislación vigente, en lo relativo a la financiación de los suplementos orales que pueden reembolsarse total, parcialmente o incluso no estar financiado para los usuarios[19-20].

En el caso de Estados Unidos, la política de financiación y reembolso de las grandes aseguradoras facilita que el péndulo de la prescripción de la NED, oscile claramente hacia el lado opuesto, en comparación con lo que sucede en España y en otros países. En la literatura, no está suficientemente aclarado si la gastrostomía percutánea endoscópica (PEG) en personas con demencia avanzada, disminuye el riesgo de aspiración, mejora el confort en familiares y pacientes y disminuye otras complicaciones (como las úlceras), la mortalidad o los costes asociados. Sin embargo, se ha descrito una prevalencia inapropiadamente elevada de gastrostomías en pacientes con demencia avanzada, ingresados en residencias de USA[21-22]. Posiblemente los incentivos a los hospitales, para reducir los días de estancia, los pagos a los endoscopistas por realizar la PEG, a las enfermeras por los cuidados, etc., influencian tomas de decisiones excesivamente intervencionistas entre los profesionales sanitarios[21]. En algunos centros se han implementado incluso, estrategias planificadas para reducir el uso inapropiado de gastrostomías en esta indicación[23].

Tendencias de uso y costes de los suplementos en España

Nuestro grupo ha analizado las tendencias de uso y consumo de nutrición enteral y de suplementos orales en la comunidad autónoma de Andalucía desde el año 2000 al año 2007 (ambos inclusive) y los costes generados por su prescripción (figs. 2a y 2b). Los datos proceden de la facturación de recetas públicas de los productos de nutrición enteral suministrados por la Consejería de Salud

(Subdirección de Prestaciones). Para los cálculos empleamos la metodología de las dosis-diarias-definidas[24]. No tuvimos en cuenta los productos categorizados como tratamientos dietoterápicos complejos (para pacientes que padezcan determinados trastornos metabólicos congénitos) pero sí los módulos nutricionales (incluyendo espesantes). En los años evaluados, el consumo de nutrición enteral domiciliaria (sumando todos los tipos de formulaciones) aumentó notablemente, multiplicándose los costes generados por 37 en 7 años, pasando de 1,3 millones de euros en el año 2.000 a más de 37 millones (año 2007). Aunque el número de personas diarias que consumieron suplementos fue mayor durante todos los años evaluados, los costes derivados de los suplementos superaron a los de las dietas por sonda sólo a partir del año 2005, debido a la combinación de dos factores: incremento progresivo del número de personas a las que se les prescriben suplementos y, por otro lado, por la incorporación de formulaciones específicas más caras. En los últimos años se constató, además, un incremento progresivo del consumo de espesantes (aunque con escasa repercusión en los costes globales). Estos datos parecen reflejar bien el consumo en España, ya que Andalucía, supone aproximadamente el 40% del coste total de la facturación por recetas.

Considerando sólo el año 2007, la prescripción de nutrición enteral domiciliaria (incluyendo enteral por sonda, suplementos, módulos y espesantes) supuso el 2,29% de los costes directos generados por la facturación de recetas públicas en Andalucía. De ellos, aproximadamente la mitad correspondieron a la prescripción de suplementos orales. Como se puede apreciar en la figura 3, en la que se refleja la distribución de los costes en el año 2007 generados por los suplementos en Andalucía, el 23% de los mismos corresponden a productos diseñados para personas con diabetes y el 10% a suplementos para pacientes con caquexia oncológica. También hemos evaluado, empleando la misma metodología, el consumo de suplementos orales en el conjunto del estado Español, a partir de los datos suministrados por la empresa IMS. El coste total generado por los suplementos fue de casi 51 millones de euros, de los que el 22% de los mismos corresponden a suplementos diseñados para personas con diabetes y el 19% para pacientes con caquexia oncológica. Posiblemente, una prescripción de los suplementos orales específicos guiada únicamente por el perfil teórico del producto y no basada en las guías de práctica clínica[25-27], podría estar incrementando el coste en determinadas indicaciones, para las que no han sido suficientemente testadas, y disminuyendo la eficiencia de la misma.

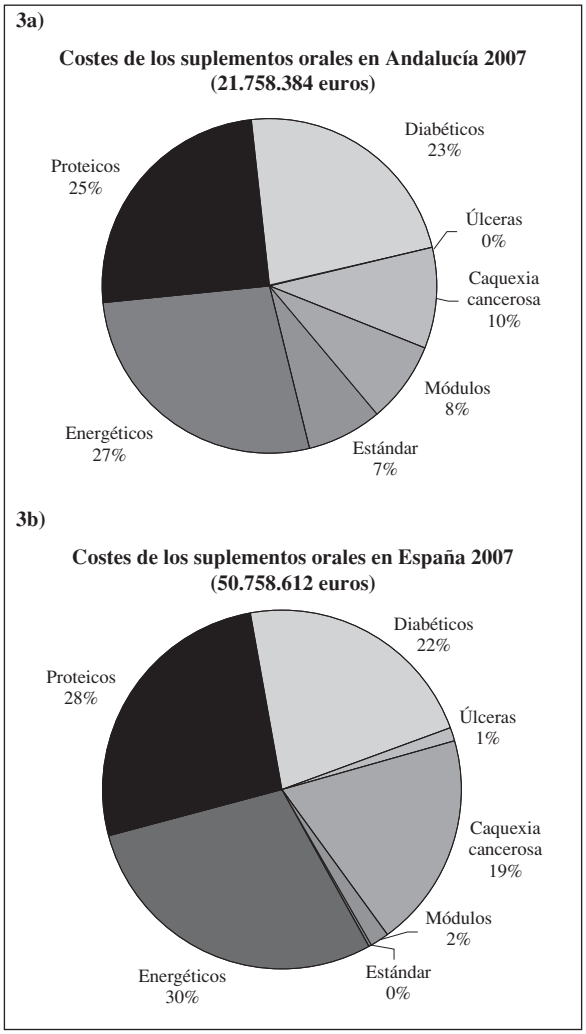

Fig. 3.—Contribución (en porcentaje) a los costes generados por la facturación de suplementos orales (más módulos nutricionales) en Andalucía y España (2007). Los datos de Andalucía proceden de la facturación de recetas públicas (Consejería de Salud de la Junta de Andalucía). Los datos del total Español proceden de los datos de mercado suministrados por IMS).

¿Es coste-efectivo el uso de suplementos orales?

Los suplementos orales mejoran la ingesta, el estado nutricional e incluso la funcionalidad y la calidad de vida de los pacientes con patologías agudas o crónicas[28]; no obstante, existen mayores dudas sobre si, además, son capaces de mejorar el pronóstico (disminuir morbimortalidad). Para poder realizar análisis de costes entre distintas opciones terapéuticas es necesario que se incluyan en los estudios variables a las que se les pueda asignar un valor económico (no sólo parámetros funcionales, de calidad de vida o nutricionales). Sin embargo, en la literatura existen muy pocos trabajos que evalúen el empleo de los suplementos orales que además sean: aleatorizados y con número suficiente de pacientes, a largo plazo, que evalúen aspectos con impacto económico (mortalidad, morbilidad, ingresos, reingresos y estancias hospitalarias, atención en urgencias, frecuentación al médico y enfermería, asistencia a domicilio…) y que, además, incluyan una evaluación económica. Por ello, como veremos posteriormente, es muy difícil sacar conclusiones definitivas, especialmente con sujetos que reciben los suplementos a nivel ambulatorio.

Coste-efectividad de los suplementos orales en personas hospitalizadas

En un artículo reciente, Russel[17] realizó un análisis de costes sobre el uso de suplementos orales comparados con tratamiento convencional en pacientes hospitalizados. Para ello analizó únicamente trabajos aleatorizados o cruzados publicados hasta el año 2004. Para estimar los costes contabilizó los suplementos consumidos y el número de días de estancia y complicaciones (pero no incluyó datos de posible ahorro por mortalidad evitada). A estos conceptos les asignó un coste estandarizado (por suplemento, estancia o complicación mayor o menor) en función de los datos en el Reino Unido para el año 2003.

Pacientes quirúrgicos

Russel[17], tras incluir a seis artículos en los que se empleaba suplementación oral en pacientes sometidos a cirugía (sobre todo abdominal)[29-34], observó un ahorro neto de unos 897 euros por paciente con el uso de la misma si se estimaba mediante descenso de estancias y de 253 euros si se estimaba por reducción de complicaciones durante el ingreso. En otros dos trabajos[35-36] realizados en pacientes sometidos a cirugía traumatológica (fracturas de caderas) también se observó que la suplementación oral era coste-efectiva con ahorros de entre 550 y 5.600 euros por reducción de estancias y entre 550 y 1.100 euros por reducción de complicaciones.

El grupo de Braga y cols.[37], demostró, en un estudio realizado en un solo centro, que el empleo durante 5 días de un suplemento con inmunonutrientes preoperatoriamente en pacientes sometidos a cirugía abdominal programada (independientemente de su estado nutricional) y comparado con el tratamiento convencional (no suplementación), era claramente coste-efectivo con un ahorro neto de 3.260 euros por paciente derivado del descenso de complicaciones.

La suplementación oral de corta duración previo a la admisión hospitalaria para cirugía electiva facilitó, en otros tres trabajos recogidos en la revisión de Russell[30,33,38], una reducción neta de costes de unos 860 euros (estimado en función de la reducción de estancias).

Pacientes de área médica o mixta

Russel[17] incluyó dos estudios realizados en pacientes hospitalizados en plantas geriátricas generales[39-40], uno en pacientes neurológicos tras ACV[41] y otro en plantas mixtas[42]. En tres de ellos el análisis de costes derivó en un ahorro neto de 418 a 2.692 euros por paciente en función del descenso de estancias o de unos 148 euros, si se estimaba por reducción de complicaciones. No obstante, en el estudio realizado en plantas medicoquirúrgicas se observó un incremento notable de los costes con el uso de la suplementación de 1674,3 euros por paciente, estimando los mismos en función de estancias.

En el año 2005, se publicó el estudio FOOD[43]. En este macro trabajo (con más de 4.000 pacientes aleatorizados) no se objetivaron beneficios de la suplementación sistemática de los pacientes que sufrieron un ACV y que podían deglutir, en cuanto a mortalidad, descenso de estancias o complicaciones. No obstante, sólo un 8% de los mismos fue considerado como desnutrido, existiendo publicaciones que señalan que los suplementos, especialmente en ancianos, serían más efectivos (y posiblemente, por tanto, más coste-efectivos) sólo en desnutridos[44-45].

El NICE[46] ha realizado una evaluación del uso de suplementos objetivando en un meta-análisis (suplementos vs tratamiento convencional) que producen un descenso significativo de las complicaciones y de la mortalidad, pero no de las estancias hospitalarias. Además, realizaron una evaluación económica del uso de suplementos orales en personas ancianas, en el contexto de un programa universal de cribado de la desnutrición hospitalaria, y concluyeron que, posiblemente sea una actuación claramente coste-efectiva en términos de costes por año de vida ganados ajustados por calidad de vida. No obstante, comentan que los estudios aleatorizados y controlados disponibles son de insuficiente calidad como para estimar los costes con adecuada precisión. Por otro lado el NICE critica el estudio de Russell, ya que estiman los costes sobre todo a partir de descenso de estancias (datos no corroborados por el NICE) y por que no incluyen otros costes en el cómputo de los gastos.

Coste-efectividad de los suplementos orales en pacientes ambulatorios

Hasta la fecha sólo se han publicado dos estudios aleatorizados que evalúan el impacto económico del uso de suplementos nutricionales orales en la comunidad. En el estudio de Edington y cols.[47], realizado en el Reino Unido, se comparó el uso de suplementos orales tras el alta hospitalaria en pacientes ancianos desnutridos (n = 51), frente al tratamiento convencional durante ocho semanas (n = 49). El objetivo era valorar si se reducían los costes directos generados (que incluían visitas al médico de primaria, visitas a domicilio médicas y de enfermería, ingresos hospitalarios, y otros). El periodo de observación fue de seis meses tras el alta y comparándolo con el mismo periodo de tiempo previo al ingreso. A pesar de que los parámetros nutricionales mejoraron ligeramente en el grupo suplementado a los seis meses, sorprendentemente se observaron incrementos significativos de los costes derivados, respecto al grupo control, debido a un mayor número de admisiones hospitalarias en los pacientes que requirieron rehospitalización. No obstante, no se observaron

diferencias en los costes totales. Tampoco mejoró la calidad de vida y la fuerza muscular (dinamometría de mano), que aunque aumentó en el grupo suplementado tras las primeras 8 semanas, volvió a su valor inicial posteriormente.

En otro trabajo del grupo de Arnaud-Battandier[48], se valoraron los costes generados por la atención a pacientes ancianos malnutridos y la repercusión del uso de suplementos orales durante 12 meses. Se basó en una comparación prospectiva de dos cohortes de pacientes atendidos en distintas zonas sanitarias con una alta (n = 186) o baja (n = 125) prescripción de suplementos orales. Los pacientes en el grupo con mayor consumo de suplementos generaron mayor coste por la prescripción de los mismos (diferencia respecto al grupo control de 528 euros) y mejoraron significativamente la puntuación del Mini Nutritional Assessment. En el cómputo global, redujeron el número de admisiones hospitalarias (con un ahorro total respecto al grupo control de 551 euros) y las consultas a médicos de familia y enfermeros (ahorro de 155 euros). Sin embargo, no se observaron reducciones estadísticamente significativas en los costes totales (sólo se objetivó un ahorro neto en el grupo total de 195 euros), ni en la mortalidad o en otras variables evaluadas.

Aunque no se han publicado otros trabajos en la literatura que incluyan una evaluación económica del uso ambulatorio de suplementos, existen estudios que analizan variables clínicas de resultados (complicaciones, mortalidad) que pueden ser traducidas a costes y otros, en los que no es fácil separar la evaluación de costes ambulatorios y hospitalarios. Por ejemplo, Beattie y cols.[32] y Smedley y cols.[30], evaluaron la continuación a nivel ambulatorio de los suplementos orales iniciados en el ámbito hospitalario (a corto plazo), estimándose ahorros económicos en función de la reducción de costes asociados al descenso de estancias en el Hospital (unos 900 euros por paciente), pero con pequeñas reducciones (81 euros) o incluso incrementos (100 euros) si se estimaban en función de las complicaciones[7].

También Stratton y cols.[28], en una "revisión de revisiones" sobre el uso de suplementos orales, concluye que, tanto las evaluaciones sistemáticas como los metaanálisis, consistentemente indican un menor número de complicaciones asociadas al uso de suplementos, incluyendo reducción de infecciones y úlceras por presión siendo los beneficios más evidentes en pacientes hospitalizados (como ya se comentó) y en pacientes dados de alta desde el hospital al ámbito comunitario. Son necesarios, por el contrario, más estudios (y mejor diseñados) sobre el efecto de los suplementos sobre la morbimortalidad (y costes) en pacientes ambulatorios con patologías específicas (como cáncer, insuficiencia respiratoria, enfermedad pulmonar obstructiva crónica, fibrosis quística, enfermedad hepática, y otras). Es importante resaltar que los datos derivados de los estudios en pacientes hospitalizados no deben ser extrapolados a los pacientes ambulatorios. Recientemente se ha publicado un trabajo aleatorizado con 80 pacientes que recibieron suplementos orales junto con consejo dietético (n = 38) durante tres meses vs no suplementación y consejo (n = 42), en sujetos dados de alta hospitalaria por patología gastrointestinal no neoplásica[49]. El peso y la masa libre de grasa mejoró en ambos grupos significativamente. No obstante la dinamometría de mano y la calidad de vida mejoró únicamente en el grupo suplementado. Aunque no se incluyó una evaluación económica, las personas suplementadas tuvieron menos readmisiones que los no suplementados. El grupo de Salas-Salvadó[50] demostró sólo mejoría de parámetros nutricionales en ancianos con Alzheimer suplementados con una dieta oral modificada basada en alimentos liofilizados (n = 24) *vs* consejo dietético (n = 29), pero sin encontrar diferencias en el MNA, las hospitalizaciones o la mortalidad.

Como se deriva de las líneas precedentes, son necesarios más trabajos y mejor diseñados para poder incluir las evaluaciones económicas en la toma de decisiones clínicas respecto al empleo de suplementos orales, especialmente en pacientes ambulatorios. No obstante la ausencia de evidencia no implica, necesariamente, la evidencia de ausencia.

Conclusiones

El empleo de suplementos orales parece ser coste/efectivo en pacientes quirúrgicos hospitalizados (en el pre y post operatorio) y, posiblemente, en ancianos malnutridos hospitalizados, especialmente tras realización de cribado de desnutrición. Aunque podrían ser eficaces, en otras circunstancias, especialmente en pacientes ambulatorios, son necesarios más trabajos con metodología adecuada, para poder realizar decisiones clínicas basadas en la evidencia y en los análisis de costes.

Referencias

1. Beauchamp BL, Walters LR, eds. Contemporary Issues in Bioethics. 2ª ed. Belmont: Wadsworth Publishing Company; 1982.
2. Evidence-Based Medicine Working Group. Evidence-based medicine. A next approach to teaching the practice of medicine. *JAMA* 1992; 268: 2420-2425.
3. Gracia D. Fundamentos de Bioética. Madrid: Endema;1989.
4. Drummond MF. Cost-of-illness studies: a major headache? *Pharmacoeconomics* 1992; 2: 1-4.
5. Olveira G, Carral F. Costes de la diabetes: una reflexión desde la situación asistencial en España. *Av Diabetol* 2000; 16: 121-130.
6. O'Brien B, Drummond M, Richardson WS, Levine M, Heyland D, Guyatt G. Economic analysis. In: Guyatt G, Rennie D, eds. Users' guides to the medical literature. Chicago: AMA Press; 2002, 621-44.
7. Russell CA. The impact of malnutrition on healthcare costs and economic considerations for the use of oral nutritional supplements. *Clin Nutr* 2007; 2: 25-32.
8. Pérez de la Cruz A, Lobo Támer G, Orduña Espinosa R, Mellado Pastor C, Aguayo de Hoyos E, Ruiz López MD. Desnutrición en pacientes hospitalizados: prevalencia e impacto económico. *Med Clin (Barc)* 2004; 123: 201-6.
9. Goiburu ME, Olveira G, Soriguer y cols. Mortalidad y morbilidad asociados a malnutrición hospitalaria. *Endocrinol Nutr* 2001; 48: 51.

10. De Luis Román D, Aller de la Fuente R, Cuéllar Olmedo LA y cols. Nutrición enteral: costes directos en su hospital terciario. Rev Clin Esp 2004; 204: 98-100.
11. De Luis Román D, Aller de la Puente R, de Luis Román J, Cuéllar Olmedo LA, Terroba Larumbe MC, Izaola Jauregui O. Nutrición enteral domiciliaria, análisis de eficiencia de un Área de Salud. *Rev Clin Esp* 2003; 203: 317-20.
12. Castillo Rabaneda RM, Gómez-Candela, De Cos Blanco AI, González Fernández B, Iglesias Rosado C. Evaluation of the cost of home enteral nutrition in relation to different access routes. *Nutr Hosp* 1998; 13: 320-4.
13. Castaño Escudero A, Pérez Gabarda ME. Nutrición enteral domiciliaria en la comunidad de Madrid. *Nutr Hosp* 2004; 19: 68-72.
14. García de Lorenzo A, Álvarez J, Calvo MV y cols. V Foro de Debate SENPE. Problemática actual de la nutrición artificial domiciliaria y ambulatoria. *Nutr Hosp* 2008; 23: 81-84.
15. RD 1.030/2006, 15 de septiembre de 2006 (BOE, 16 de septiembre, 2006).
16. Orden SCO/3.858/2006, 5 de diciembre de 2006 (BOE, 20 de diciembre, 2006).
17. Cuerda C, Chicharro ML, Frías L y cols. Registro de la nutrición enteral domiciliaria en España en el año 2006 (Grupo NADYA-SENPE). *Nutr Hosp* 2008; 23: 95-99.
18. Olveira G, Muñoz A. Importancia del soporte nutricional ambulatorio. En: Escobar L y Aguilar M (dir). Nutrición y Hormonas. Madrid: Ergón ediciones SA, 2001: 373-385.
19. Moreno Villares JM. La práctica de la nutrición artificial domiciliaria en Europa. *Nutr Hosp* 2004; 19: 59-67.
20. Moreno JM, Shaffer J, Staun M y cols. Home Artificial Nutrition Working Group-ESPEN. Survey on legislation and funding of home artificial nutrition in different European countries. *Clin Nutr* 2001; 20: 117-23.
21. Finucane TE, Christmas C, Leff BA. Tube feeding in dementia: how incentives undermine health care quality and patient safety. *J Am Med Dir Assoc* 2007; 8: 205-8.
22. Mitchell SL, Buchanan JL, Littlehale S, Hamel MB. Tube-feeding versus hand-feeding nursing home residents with advanced dementia: a cost comparison. *J Am Med Dir Assoc* 2004; 5 (Supl. 2): 22-9.
23. Monteleoni C, Clark E. Using rapid-cycle quality improvement methodology to reduce feeding tubes in patients with advanced dementia: before and after study. BMJ 2004 28;329:491-4.
24. Olveira Fuster G, García García-Doncel L, Carral SanLaureano F, Domenech Cienfuegos I, Arencibia Rivero T, Manzano Martín MV. Dispensación de los productos dietoterapéuticos mediante dosis unitarias en un hospital universitario: efectos sobre el consume y costes. *Nutr Hosp* 2000; 15: 58-63.
25. ASPEN Board of Directors and The Clinical Guidelines Task Force. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. *JPEN* 2002; 26 (Supl. 1): 22-32.
26. Bellido D, Ballesteros, Álvarez J, del Olmo D. Nutrición basada en la evidencia (monográfico). *Endocrinol Nutr* 2005; 52 (Supl. 2): 1-114.
27. Valentini L, Schütz T, Allison SP, Howard P, Pichard C, Lochs C. ESPEN Guidelines on adult enteral nutrition. *Clin Nutr* 2006; 25: 177-360.
28. Stratton RJ, Elia M. A review of reviews: A new look at the evidence for oral nutritional supplements in clinical practice. *Clin Nutr* 2007; 18 (Supl. 2): 29-84.
29. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, Frost P y cols. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr* 1992; 11: 337-44.
30. Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O y cols. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* 2004; 91: 983-90.
31. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomized controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut* 2000; 46: 813-8.
32. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut* 1997; 40: 393-7.
33. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. *Nutrition* 2000; 16: 723-8.
34. Saluja SS, Kaur N, Shrivastava K. Enteral nutrition in surgical patients. *Surg Today* 2002; 32: 672-8.
35. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, Bonjour J-P. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet* 1990; 335: 1013-6.
36. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr* 2003; 22: 39-46.
37. Braga M, Gianotti L. Preoperative immunonutrition: cost-benefit analysis. *J Parenter Enteral Nutr* 2005; 29: S57-S61.
38. Flynn MB, Leightty FF. Preoperative outpatient nutritional support of patients with squamous cancer of the upper aerodigestive tract. *Am J Surg* 1987; 154: 359-62.
39. Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients: a randomized controlled trial. *J Parenter Enteral Nutr* 2001; 25: 323-9.
40. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, Albert A y cols. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing* 2003; 32: 321-5.
41. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomised controlled single-blind trial of nutritional supplementation after acute stroke. *J Parenter Enteral Nutr* 1998; 22: 315-9.
42. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, Obeid OA y cols. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr* 2001; 20: 517-26.
43. Dennis MS, Lewis SC, Warlow C; FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet* 2005; 365: 755-63.
44. Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. *Ann Intern Med* 2006; 144: 37-48.
45. Koretz RL, Avenell A, Lipman TO, Braunschweig CL, Milne AC. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am J Gastroenterol* 2007; 102: 412-29.
46. National Collaborating Centre for Acute Care, February 2006. Nutrition support in adults Oral nutrition support, enteral tube feeding and parenteral nutrition. National Collaborating Centre for Acute Care, London. Available from www.rcseng.ac.uk
47. Edington J, Barnes R, Bryan F, Dupree E, Frost G, Hickson M y cols. A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. *Clin Nutr* 2004; 23: 195-204.
48. Arnaud-Battandier F, Malvy D, Jeandel C, Schmitt C, Aussage P, Beaufrere B y cols. Use of oral supplements in malnourished elderly patients living in the community: a pharmaco-economic study. *Clin Nutr* 2004; 23: 1096-103.
49. Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease – a randomized controlled trial. *Clin Nutr* 2008; 27: 48-56.
50. Salas-Salvadó J, Torres M, Planas M y cols. Effect of oral administration of a whole formula diet on nutritional and cognitive status in patients with Alzheimer's disease. *Clin Nutr* 2005; 24: 390-7.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):260-272
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Interacción de los antineoplásicos orales con los alimentos: revisión sistemática

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Resumen

Introducción: **Los estudios de biodisponibilidad son parte integrante del desarrollo clínico de medicamentos para administración oral con el fin de identificar potenciales interacciones fármaco-alimento (iFA). Actualmente, para los antineoplásicos orales se empieza a reconocer su importancia clínica, aun cuando lamentablemente, la información disponible presenta variabilidad en su evidencia científica.**

Objetivos: **Revisar la evidencia científica disponible sobre las interacciones de los alimentos con medicamentos antineoplásicos orales y establecer recomendaciones para su administración.**

Métodos: **Se realizó una búsqueda bibliográfica en Medline y The Cochrane Library para el periodo comprendido entre enero de 1966 a marzo de 2008, enfocada a identificar las publicaciones sobre interacciones fármaco alimento con antineoplásicos orales. El análisis bibliográfico consta de dos fases. En la primera fase se excluyeron los artículos que por título y contenido del resumen no se correspondían con el objetivo planteado; en la segunda fase se eliminaron las referencias duplicadas en ambas bases de datos.**

Los criterios de inclusión para seleccionar los artículos fueron: diseño (revisiones sistemáticas, metaanálisis, ensayos clínicos randomizados Fase I y II), población (pacientes adultos; >19 años de edad), intervención evaluada (administración de antineoplásicos orales bajo condiciones de ayuno o con alimentos) y medida del resultado de la iFA (cálculo del IC90% de la razón entre la media geométrica de valores del área bajo la curva de concentraciones plasmáticas (ABC) o la concentración plasmática máxima (Cmax) con y sin alimentos). Se excluyeron las publicaciones que como medida de resultado no hacían referencia al dictamen de bioequivalencia establecido por la Food and Drugs Administration (FDA). La

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Recibido: 18-IX-2008.
Aceptado: 2-II-2009.

ANTINEOPLASTIC ORAL AGENTS AND DRUG-NUTRIENT INTERACTIONS: A SISTEMATIC REVIEW

Abstract

Introduction: **studies on bioavailability are part of the clinical development of drugs for oral use in order to identify potential drug-food interactions. For oral antitumor drugs, their clinical importance is currently recognized although regrettably the information available presents variability concerning the scientific evidence.**

Objectives: **To review the available scientific evidence about oral anti-tumor medications and establish the recommendations for their administration with foods.**

Methods: **We carried out a bibliographic search in Medline and The Cochrane Library for the period January of 1966 to March of 2008, focused on identifying those publications about drug-food interactions with oral antitumor medications. The bibliographical analysis was made in two steps. During the first phase, we excluded those articles in which the title or their content did not correspond with the objective settled; during the second phase, we deleted all the references duplicated in both databases.**

The inclusion criteria to select the articles were: design (systematic reviews, meta-analysis, Phase I and Phase II randomized clinical trials), population (adult patients; >19 years of age), intervention evaluated (administration of oral anti-tumor drugs under fasting conditions or with food) and measurement of the iFA results (calculation of the 90% CI of the odds ratio between the geometric mean of the values under the curve of the plasma concentrations (ABC) or the maximal plasma concentration (Cmax) with and without foods). We excluded those publications that did not make reference to the bioequivalence dictamen established by the Food and Drugs Administration (FDA) in their outcomes measurement. A critical appraisal of the selected articles was done according to the recommendations that the FDA established to be met by these studies.

Results: **At the initial search we obtained 850 references (98.5% Medline + and 1.4% Cochrane). During the first phase, we excluded 87.7% (746) of the articles, 100% of them corresponding to the search in Medline. During**

valoración crítica de los artículos seleccionados se realizó según las recomendaciones que de acuerdo con la FDA deben cumplir estos estudios.

Resultados: **En la búsqueda inicial se obtuvieron 850 referencias (98,5% Medline + y 1,4% Cochrane). En la primera fase se excluyeron el 87,7% (746) de los artículos, correspondiendo el 100% a la búsqueda en Medline. En la segunda fase, quedaron 40 artículos (5,2% de los iniciales) para su lectura crítica a texto completo, a los que se añadieron cuatro más no indexados en Medline.**

De la lectura crítica de los 44 artículos finales, se excluyeron 25 artículos (20 artículos originales, 4 comunicaciones cortas y 1 metanálisis) por no incluir como medida de resultado el dictamen de bioequivalencia. Los 19 (2,2%) artículos restantes proporcionaron información sobre 19 fármacos antineoplásicos orales, en 210 pacientes y 146 voluntarios sanos. De estos 19 fármacos, el 63% no presentan iFA o interacciones fármaco-alimento, pudiéndose administrar indistintamente con/sin alimentos; el 21% se deben administrar con alimentos y sólo el 16% presentan interacción fármaco alimento, por lo que se deben administrar sin alimentos.

Discusión: **Actualmente, la importancia clínica de las interacciones fármaco alimento con antineoplásicos orales se identifica más directamente con la seguridad del paciente que con la efectividad del tratamiento.**

Ante el desarrollo de estos agentes orales, su irrupción en la terapia oncológica desplazando a la terapia parenteral, con costes mensuales de miles de euros, hay necesidad de realizar estudios farmacocinéticos y farmacodinámicos bien diseñados. Su objetivo debe de ser comparar su biodisponibilidad en presencia o ausencia de alimentos con la respuesta clínica. Mientras tanto, establecer recomendaciones para su administración en relación con los alimentos, es inconsistente para algunos de estos fármacos y su resultado incierto por la falta de estudios fundamentados en el dictamen de bioequivalencia establecido por la FDA.

(*Nutr Hosp*. 2009;24:260-272)

Palabras clave: *Agentes antineoplásicos. Efecto de los alimentos. Quimioterapia oral. Farmacocinética. Revisión sistemática.*

the second phase, 40 studies remained (5.2% of the initial ones) for full-text critical appraisal, to which four studies were added not indexed in Medline.

From the critical appraisal of the 44 final articles, 25 were excluded (20 original articles, 4 short communications, and 1 meta-analysis) because they did not include as an outcome measure the bioequivalence dictamen. The 19 (2.2%) remaining articles provided information on 19 oral anti-tumor drugs in 210 patients and 146 healthy volunteers. Of these 19 drugs, 63% did not present drug-food interactions, with the possibility of administering them either with or without food; 21% have to be administered with foods and only 16% present drug-food interactions, so they have to be administered without foods.

Discussion: **Currently, the clinical importance of drug-food interactions with oral anti-tumor drugs is identified more directly with the patient's safety than with the efficacy of the therapy. Given the development of these oral agents, their incorporation into the oncologic strategy displacing parenteral therapy, with monthly costs of thousands of Euros, it is necessary to perform well-designed studies on pharmacokinetics and pharmacodynamics. Their goal has to be comparing their bioavailability in the presence or absence of foods with the clinical response. In the meanwhile, to establish recommendations for their administration in relation to foods is inconsistent for some of these drugs and their results is uncertain given the lack of studies based on the FDA bioequivalence dictamen.**

(*Nutr Hosp*. 2009;24:260-272)

Key words: *Anti-tumor agents. Effects of foods. Oral chemotherapy. Pharmacokinetics. Systematic review.*

Introducción

La administración de medicamentos durante las comidas, media hora antes y hasta una hora después de las mismas, puede ser causa de elevada variabilidad en la respuesta clínica por interacción entre los fármacos y los alimentos (iFA) o alguno de sus componentes[1,2]. Este proceso se inicia en alguna de las partes del tracto gastrointestinal y a veces se enmascara con la enfermedad o con otros tipos de interacción entre los fármacos que componen el tratamiento farmacológico, dificultando su verdadera interrelación con el riesgo de toxicidad o fracaso terapéutico. Por esta razón u otras que no alcanzamos a identificar, actualmente las iFA se siguen considerando de escaso interés clínico[3,4].

La terapia antineoplásica oral (hormonal y citostática) representa que los casos incidentes aumenten año tras año hasta situarse en no menos del 15% de los pacientes tratados con esta terapéutica. La comodidad de estos regímenes para el paciente ambulatorio es una realidad porque no compromete el resultado clínico, pero no se debe olvidar que son fármacos de estrecho margen terapéutico, a menudo administrados en combinación con otros agentes de similares características y sujetos a iFA. Además, los regímenes de dosificación de estos medicamentos son, en su mayoría, más complejos que los manejados en la farmacoterapia convencional de modo que en un contexto ambulatorio, la auto-administración por el paciente o cuidador, sin una información y monitorización predeterminada, puede traducirse en una falta de adherencia a los mismos.

Los pacientes, en general, no presentan idéntica respuesta a un mismo tipo de iFA[5] por lo que las modificaciones farmacocinéticas deben analizarse considerando la posibilidad de que algunos alimentos, al alterar la actividad de enzimas de trasporte o metabolizadores, modifiquen la respuesta antineoplásica a estos fármacos[6]. Por tanto, al igual que sucede con las interacciones fármaco-fármaco, la significación clínica de las iFA se manifiesta con elevada variabilidad, baja

prevalencia (1% del total) y con gravedad escasa o nula en el 40% de los casos, moderada en un 50% y grave en menos del 10% de las iFA[7].

Los estudios de biodisponibilidad son parte integrante en las fases tempranas del desarrollo clínico de medicamentos para administración oral, pero en el caso de los antineoplásicos orales, las iFA no están claramente definidas, clasificadas y caracterizadas[8,9]. Actualmente, se empieza a reconocer su importancia clínica, planteándose su estudio con la misma metodología que soporta los ensayos clínicos[10,11] ya que proporciona la mejor evidencia científica en fases tempranas[12,13]. Lamentablemente, la información disponible sobre las más de trescientas iFA o interacciones fármaco-alimento descritas, no se fundamenta sobre este grado de evidencia[14-16].

En este trabajo se plantea una revisión sistemática sobre las iFA con medicamentos antineoplásicos orales a la vez que identifica el grado de evidencia científica disponible; su objetivo es alcanzar a poder recomendar la administración oral de estos medicamentos con alimentos, sin alimentos o indistintamente, desde la información publicada y revisada.

Métodos

Tipo de estudio

Revisión sistemática de la evidencia científica disponible, desde enero de 1966 a marzo de 2008, relacionada con las iFA con antineoplásicos orales comercializados o en fase de investigación.

Bases de datos y búsqueda bibliográfica

Se realizó la búsqueda bibliográfica a partir de la pregunta "iFA con los antineoplásicos orales comercializados" en las bases de datos Medline y The Cochrane Library. Como palabras clave se utilizaron: "antineoplastic agents, food effect, oral chemotherapy, food-drug interaction, pharmacokinetics".

Antes de aplicar los criterios de selección de artículos se establecieron dos fases. La primera fase tuvo como objetivo seleccionar sólo los artículos que, por título y contenido del resumen, se correspondían con la pregunta de investigación. En la segunda fase, se eliminaron las referencias duplicadas al reunir las referencias de las dos fuentes manejadas.

Criterios de selección de los artículos

Inclusión:

1. Tipo de estudios:
   a) Revisiones sistemáticas.
   b) Metaanálisis.
   c) Ensayos clínicos randomizados (Fase I y II).
2. Población de pacientes:
   a) Pacientes adultos (> 19 años de edad).
3. Intervenciones a comparar:
   a) Administración de antineoplásicos orales bajo condiciones de ayuno o con alimentos.
4. Medida de resultado:
   a) Cálculo del IC90% de la razón entre la media geométrica de valores de ABC y Cmax con alimentos y en condiciones de ayuno.

Exclusión:

1. Publicaciones que como medida de resultado no hacían referencia al dictamen de bioequivalencia establecido por la FDA[17]; esto es, los límites (superior e inferior) del intervalo de confianza de la razón entre la media geométrica de valores de ABC o Cmáx, con alimentos y en condiciones de ayuno, han de estar comprendidos entre 0,8-1,25, para valores logotransformados (escala semilogarítmica) porque no es posible establecer la presencia de iFA, ni su relevancia clínica o bioinequivalencia.

$$0{,}8 > \frac{ABC_{conA}}{ABC_{ayuno}} > 1{,}25$$

Evaluación crítica de los estudios seleccionados

Se ha realizado la valoración crítica de los artículos seleccionados según las recomendaciones que, de acuerdo con la FDA[17], deben cumplir estos estudios (Anexo 1).

Resultados

La búsqueda bibliográfica proporcionó 850 referencias (98,5% (838) Medline + y 1,4% (12) Cochrane). En la primera fase de revisión se excluyeron el 87,7% (746) de los artículos, correspondiendo el 100% a la búsqueda procedente de Medline. Durante la segunda fase fueron eliminadas las referencias duplicadas en ambas bases de datos. El resultado final de la búsqueda bibliográfica (tabla I) fue de sólo 40 artículos (5,2% de los iniciales) que se sometieron a lectura crítica a texto completo. A este proceso se añadieron 4 artículos más no indexados en Medline.

La lectura completa de los 44 trabajos seleccionados permitió identificar 25 referencias (20 artículos originales, 4 comunicaciones cortas y 1 metanálisis), que como medida del resultado en la población de estudio no consideraban el dictamen de bioequivalencia por lo que finalmente fueron excluidos. En la tabla II se recogen algunas de las características más destacables de los 19 artículos restantes (2,2% del total de la búsqueda inicial) que cumplen los criterios de inclusión predeterminados en este trabajo de revisión.

Tabla I
Búsqueda bibliográfica inicial en Medline y Cochrane (marzo 2008)

Palabras clave	*Número de referencias identificadas*					
	Medline			*Cochrane Library*		
	Búsqueda inicial	*1.ª fase*	*2.ª fase*	*Búsqueda inicial*	*1.ª fase*	*2.ª fase*
Antineoplastic agents and food effect	533	35	35	3	3	0
Antineoplastic agents and food effect and pharmacokinetics	112	28	0	3	3	0
Oral chemotherapy and food effect and pharmacokinetics	154	17	2	0	0	0
Antineoplastic agents and food-drug interaction	39	12	3	6	6	0
Total	838	92	**40**	12	12	**0**

Límites de búsqueda en Medline: Humanos, adultos > 19 años. Desde 1966 hasta marzo de 2008.
1ª fase: se excluyen aquellos artículos que por título y resumen no se corresponden con la pregunta de investigación.
2ª fase: se excluyen referencias duplicadas dentro de cada búsqueda y entre ellas. Al final de la segunda fase quedan 40 referencias para lectura a texto completo.

En los 19 trabajos seleccionados se han totalizado 19 fármacos antineoplásicos orales diferentes que han sido ensayados en una población de 250 pacientes con cáncer y 146 voluntarios sanos. En la tabla III se recogen los valores medios y desviación estándar para el ABC y, en la tabla IV se incluyen estos mismos datos para la Cmax. En ambos casos se ha considerado la presencia o ausencia de alimentos. Se incluye el dictamen de bioequivalencia para los 19 antineoplásicos orales estudiados. De los 25 artículos excluidos es relevante destacar que un 63,6% de las publicaciones (n = 14) cuantifican la presencia de iFA mediante el cálculo del porcentaje de cambio en los valores de referencia para ABC, Cmax y Tmax.

El resultado de la iFA de los antineoplásicos orales estudiados, en relación con el tipo de alimento y el cambio identificado respecto a los valores de referencia para ABC, Cmax y Tmax, expresado en porcentaje, se describe en la tabla V. Asimismo, se indican las recomendaciones expresadas para los diferentes antineoplásicos en los artículos seleccionados. Se evidencia que el 63% de estos fármacos estarían en "condiciones ideales" para su administración oral con o sin alimentos, indistintamente, porque no se modifican de manera significativa los valores medios de ABC y Cmax en ambas condiciones. El resto de los fármacos deben administrarse siguiendo una norma respecto a la ingesta de alimentos y así, hasta un 21% de estos fármacos se recomienda su administración con alimentos y un 16% sin alimentos.

Durante el proceso de lectura crítica se identificaron publicaciones que a pesar de establecer la influencia sobre los valores ABC y Cmax, en las condiciones de estudio con alimentos y sin alimentos, no había posibilidad de dictamen de bioequivalencia porque no disponían del IC 90% de la razón de los valores ABC y Cmax en las condiciones estudiadas. La información extraída respecto al tipo de alimento, contenido graso de los mismos y el porcentaje de cambio en los valores de referencia para ABC, Cmax y Tmax se describen en la tabla VI.

De los 19 fármacos antineoplásicos orales estudiados con el objetivo de establecer la presencia o ausencia de iFA, únicamente para el 42% se puede demostrar la condición de bioequivalencia; es decir, se cumple el criterio de que ambos límites (superior e inferior) del IC 90% del ABC están incluidos en el ámbito de valores 0,8 y 1,25. Para los 11 antineoplásicos restantes (58%) los estudios de iFA evidencian condición de bioinequivalencia; es decir, uno o los dos límites del IC 90% se sitúa por encima o por debajo del ámbito de valores aceptado para los IC90% de la razón de los parámetros medios de ABC (fig. 1) y Cmax (fig. 2) obtenidos en la situación "con o sin alimentos", para estos fármacos. Estas variaciones en el ABC o Cmax no parecen ser clínicamente determinantes ya que en la práctica asistencial no se utiliza el criterio de bioequivalencia para las iFA; tampoco parece existir evidencia para establecer el grado de correlación entre este dictamen y su respuesta en el paciente[20].

Discusión

En los últimos años se ha incrementado el entusiasmo por el desarrollo de los agentes antineoplásicos vía oral, de nueva síntesis o a partir de fármacos parenterales ya comercializados[18,19] dadas las implicaciones tanto clínicas como económicas de esta vía oral versus la vía parenteral. Pero el desarrollo de fármacos vía oral requiere un mayor conocimiento de los múltiples factores que pueden afectar a su biodisponibilidad: los alimentos, la dosis y cualquier otra medicación oral administrada concomitantemente.

Tabla II
Descripción de los estudios seleccionados, diseño, medicamento y población incluida

Autores, año de publicación	*Diseño de los Ensayos Clínicos*	*Antineoplásico oral y tipo administración*	*Tipo de población y número (PK/total)*
Cockshott y cols., 1996[15]	Randomizado, cruzado (PL: 9 sem)	Bicalutamida (DU)	Adultos sanos, N = 15/15
Sioufi y cols., 1996[26]	Cruzado (PL: 4 sem)	Letrozol (DU)	Adultos sanos, N = 12/12
Teo y cols., 2000[27]	Randomizado, cruzado y abierto (PL: 1 sem)	Talidomida (DU)	Adultos sanos, N = 13/13
Valle y cols., 2005[11]	Randomizado, cruzado y abierto (PL: 4-5 sem)	Exemestano (DU)	Adultos sanos, N = 12/12
Swaisland y cols., 2005[28]	Randomizado, cruzado (PL: 3 sem)	Gefitinib (DU)	Adultos sanos, N = 26/96
Bello y cols., 2006[29]	Randomizado, cruzado y abierto. Fase I. (PL: 4 sem)	Sunitinib (DU)	Adultos sanos, N = 16/16
Zhu y cols., 2007[24]	Randomizado, cruzado. Fase I (PL: 2 sem)	Lonafarnib (DU) Lonafarnib (DM)	Adultos sanos, N = 12/12 Adultos con tumores sólidos o hematológicos, N = 19/19
Ling y cols., 2008[30]	Randomizado, cruzado, abierto (PL: 1 sem)	Erlotinib (DU) Erlotinib (DM)	Adultos sanos, N = 18/21 Adultos sanos, N = 22/36
Reigner y cols., 1998[31]	Randomizado, cruzado y abierto (PL: 1 sem)	Capecitabina (DM)	Adultos con cáncer colorrectal, N = 11/11
Revén y cols., 1999[32]	Randomizado, cruzado y abierto (PL: 1 día)	Topotecan (DU)	Adultos con tumores sólidos, N = 18/18
Eskens y cols., 2000[33]	Fase I.	MM1270B (DU)	Adultos con tumores sólidos, N = 17/17
Damle y cols., 2001[34]	Randomizado, cruzado (PL: 3 días)	UFT (DU)	Adultos con tumores sólidos, N = 25/25
Bugat y cols., 2002[10]	Randomizado, cruzado y abierto. Fase I. (PL: 1 sem)	Vinorelbina (DU)	Adultos con tumores sólidos o linfomas, N = 12/12
Shepard y cols., 2002[35]	Randomizado, cruzado y abierto (PL: 7 días)	5-fluorouracilo (DU)	Adultos con tumores sólidos, N = 12/12
Godefridus y cols., 2004[36]	Randomizado, cruzado (PL: 1 sem)	S-1 (DU)	Adultos con tumores sólidos, N = 18/18
Lorusso y cols., 2005[37]	Randomizado, cruzado y abierto. Fase I. (PL: 1 sem)	CI-1040 (DU)	Adultos con tumores sólidos o linfomas, N = 29/77
Soepenberg y cols., 2005[38]	Randomizado, cruzado. Fase I (PL: 21 días)	Irinotecan (DM) SN38	Adultos con tumores sólidos, N = 16/25
Kuppens y cols., 2007[39]	Randomizado, cruzado. Fase I (PL: 4 días)	Indibulina (DU)	Adultos con tumores sólidos, N = 6/14
Reddy y cols., 2007[40]	Randomizado, cruzado y abierto. Fase I	Lapatinib (DU)	Adultos con tumores sólidos, N = 27/27

PL: periodo de lavado; DU: Dosis única; DM: Dosis múltiple.
Población PK/total: población de pacientes con datos farmacocinéticos referentes a ABC y Cmax frente a pacientes totales incluidos en el estudio.
MMI270B: inhibidor de las metaloproteinasas de la matriz extracelular (MMPs), enzimas responsables de la degradación de la matriz extracelular que constituye el tejido conectivo.
UFT: fármaco compuesto por Tegafur (profármaco de 5-fluorouracilo) y uracilo (inhibidor competitivo y reversible de la enzima dihidropirimidina deshidrogenasa o DPD, responsable del catabolismo de 5-FU) en proporción molar 1:4.
S-1: formulación oral de Tegafur (profármaco de 5-fluorouracilo), 5-cloro-2,4-dihidroxipiridina (inhibidor de la dihidropirimidina deshidrogenada o DPD) y ácido oxónico (inhibidor de la fosforibosilación de 5-fluorouracilo en la mucosa intestinal) en proporción molar 1:0,4:1.
CI-1040: inhibidor selectivo de 2 kinasas específicas de la cascada de la Ras-mitogen-activated protein kinase (MAPK); MEK 1 y 2.

El conocimiento de la biodisponibilidad de antineoplásicos orales proporciona ventajas como la recientemente propuesta por Mark y cols.[20], de reducir cinco veces la dosis estándar de lapatinib cuando se administra con alimentos; esta condición no sólo disminuye el coste del tratamiento en un 80% sino la frecuencia y/o severidad de la diarrea dosis-dependiente secundaria a su administración. En consecuencia, es lógico que la detección e identificación de pacientes con oportunidades de mejora relacionadas con las iFA, sea uno de los estándares establecidos por la Joint Comision on Accreditation of Healthcare Organizations (JCAHO)[21] a la vez que se reconoce la gran dificultad de su cumplimiento. A esta situación, contribuye, negativamente, el reciente informe de la American Society for Parenteral and Enteral Nutrition (ASPEN)[22] y la Guía Clínica

Tabla III

Dictámen de bioequivalencia (BE) de la administración de antineoplásicos orales, en presencia y ausencia de alimentos. Valores medios del área bajo la curva (ABC) y desviación estándar (DE) calculados

Antineoplásico oral	*ABC (Media y DE)*				*Medidas de resultado*	*BE (0,8-125)*
	Con alimentos		*Sin alimentos*		ABC_r *(IC 90%)*	
R-Bicalutamida	157	SD	153	SD	0,97 (0,89-1,07)	Sí
S-Bicalutamida	2,1	SD	2,18	SD	1,03 (0,79-1,36)	No
CI-1040	2.520	SD	624	SD	4,65 (2,79-7,74)	No
Capecitabina	5,96	SD	8,65	SD	1,51 (1,28-1,79)	No
5'-DFCR	9,42	SD	11,9	SD	1,26 (1,02-1,54)	No
5'-DFUR	14,4	SD	16,5	SD	1,15 (0,99-1,33)	No
5-FU	0,69	SD	0,83	SD	1,13 (0,93-1,36)	No
FUH_2	4,11	SD	4,57	SD	1,07 (0,86-1,33)	No
FBAL	31,4	SD	32,4	SD	1,05 (0,94-1,15)	No
Erlotinib_DU	20.775	1.946	10.533	3.776	2,09 (1,65-2,64)	No
DM	18.823	9.298	13.739	5.436	1,34 (0,87-2,7)	No
Exemestano	41,3	3,4	29,7	2,2	1,39 (1,21-1,60)	No
5-fluorouracilo	7.061	2.226	7.740	2.162	0,97 (0,86-1,06)	Sí
Gefitinib	3.118	SD	2.281	SD	1,36 (1,24-1,51)	No
Indibulina	337	88,8	291	128	1,24 (0,96-1,61)	No
Irinotecan	SD	SD	SD	SD	1,13 (0,86-1,48)	No
SN38	SD	SD	SD	SD	1,17 (0,88-1,55)	No
Lapatinib*	60,9	SD	14,5	SD	4,25 (3,60-5,02)	No
	38,6	SD	14,5	SD	2,67 (2,26-3,16)	No
Letrozol	5.739	2.240	5.920	2.470	0,98 (0,92-1,05)	Sí
Lonafarnib_DU	1,55	60	2,07	61	0,77 (0,59-1,01)	No
DM	21,5	67	24,1	85	0,96 (0,82-1,11)	Sí
MMI270B	6.787	340,6	7.711	3.592	0,90 (0,81-0,98)	Sí
S-1						
Tegafur	5.524	SD	5.700	SD	1,00 (0,98-1,01)	Sí
Uracilo	4.171	SD	3.697	SD	0,99 (0,98-0,99)	Sí
5-Fluorouracilo	365	SD	441	SD	0,97 (0,95-0,98)	Sí
CDHP	644	SD	738	SD	0,98 (0,96-0,99)	Sí
Ácido Oxonico	107	SD	247	SD	0,83 (0,79-0,88)	No
Sunitinib	1.765	SD	1.489	SD	1,12 (1,08-1,16)	Sí
SU12662	575	SD	606	SD	0,92 (0,89-0,96)	Sí
Talidomida	23,5	3,7	24,7	5,1	0,95 (0,89-1,02)	Sí
Topotecan	73,7	28,6	68,4	29,8	0,93 (0,83-1,03)	Sí
UFT						
Tegafur	53.637	18.229	57.622	20.092	0,98 (0,91-1,05)	Sí
Uracilo	82	79	126	96	0,38 (0,25-0,60)	No
5-Fluorouracilo	82	79	126	96	0,67 (0,51-0,90)	No
Vinorelbina	373,3	125,8	444,2	183,5	0,84 (0,69-1,14)	No

ABC: área bajo la curva de concentración plasmática-tiempo (ng x h/ml); SD: sin datos; ABC_r: razón del ABC con alimentos y en ayunas.

*Valores de ABC para alimentos con alto y bajo contenido graso.

CI-1040: inhibidor selectivo de 2 kinasas específicas de la cascada de la Ras-mitogen-activated protein kinase (MAPK); MEK 1 y 2.

Metabolitos de capecitabina: 5'-DFCR (5'desoxi-5-fluorocitidina), 5'-DFUR (5' desoxi-5-fluorouridina), 5-FU (5-fluorouracilo), FUH_2 (dihidro-5-fluorouracilo), FBAL (α-fluoro-β-alanina).

SN-38: metabolito activo de Irinotecan.

MMI270B: inhibidor de las metaloproteinasas de la matriz extracelular (MMPs), enzimas responsables de la degradación de la matriz extracelular que constituye el tejido conectivo.

S-1: formulación oral de Tegafur (profármaco de 5-fluorouracilo), 5-cloro-2,4-dihidroxipiridina (CDHP: inhibidor de la dihidropirimidina deshidrogenada o DPD) y ácido oxónico (inhibidor de la fosforibosilación de 5-fluorouracilo en la mucosa intestinal) en proporción molar 1:0,4:1.

SU12662: metabolito activo de Sunitinib.

UFT: fármaco compuesto por Tegafur (profármaco de 5-fluorouracilo) y uracilo (inhibidor competitivo y reversible de la enzima dihidropirimidina deshidrogenasa o DPD, responsable del catabolismo de 5-FU) en proporción molar 1:4.

Tabla IV
Valores medios y desviación estándar (DE) de la concentración máxima (Cmax) en presencia y ausencia de alimentos, con dictámen de bioequivalencia (BE)

Antineoplásico oral	*Cmax (Media y DE)*				*Medidas de resultado*	*BE (0,8-125)*
	Con alimentos		*Sin alimentos*		*ABC_r (IC 90%)*	
CI-1040	307	SD	66,8	SD	4,56 (2,67-7,79)	No
Capecitabina	2,68	SD	6,63	SD	2,47 (1,61-3,78)	No
5'-DFCR	3,71	SD	6,68	SD	1,81 (1,34-2,43)	No
5'-DFUR	6,28	SD	9,47	SD	1,53 (1,05-2,22)	No
5-FU	0,31	SD	0,46	SD	1,58 (1,06-2,37)	No
FUH_2	1,12	SD	1,38	SD	1,26 (1,02-1,55)	No
FBAL	5,67	SD	6,19	SD	1,11 (1,01-1,22)	Sí
Erlotinib_DU	1.339	244	852	320	1,64 (1,3-2,06)	No
DM	1.426	482	1.069	331	1,33 (0,95-1,85)	No
Exemestano	17,7	4,5	11,1	1,3	0,69 (0,49-1,14)	No
Gefitinib	137,6	SD	104,4	SD	1,32 (1,16-1,49)	No
Indibulina	36,9	5,18	44,7	18	0,89 (0,55- 1,44)	No
Lapatinib*	2,9	SD	0,94	SD	3,03 (2,53-3,63)	No
	2,38	SD	0,94	SD	2,42 (2,02-2,90)	No
Letrozol	98,7	18,6	129	20,3	0,76 (0,70-0,83)	No
Lonafarnib_DU	154	50	323	55	0,48 (0,37-0,61)	No
DM	2,27	57	2,76	76	0,87 (0,75-1,02)	Sí
MMI270B	4.406	2.264	7.432	5.158	0,55 (0,45-0,77)	No
S-1						
Tegafur	7,97	SD	13	SD	0,83 (0,77-0,89)	Sí
Uracilo	5,56	SD	4,99	SD	0,94 (0,92-0,96)	Sí
5-Fluorouracilo	1,46	SD	1,6	SD	0,98 (0,95-1,00)	Sí
CDHP	2,48	SD	3,27	SD	0,95 (0,92-0,98)	Sí
Ácido Oxonico	0,35	SD	0,85	SD	0,86 (0,83-0,90)	No
Sunitinib	27,6	SD	25,1	SD	1,04 (0,97-1,11)	Sí
SU12662	3,53	SD	4,46	SD	0,77 (0,69-0,86)	No
Talidomida	2,17	0,51	1,99	0,41	1,08 (0,96-1,22)	Sí
Topotecan	10,6	4,4	9,2	4,1	0,87 (0,74-1,01)	No
UFT						
Tegafur	4.391	960	6.623	1.598	0,66 (0,61-0,73)	No
Uracilo	682	757	2.823	2.647	0,28 (0,16-0,49)	No
5-Fluorouracilo	34	42	115	116	0,34 (0,21-0,55)	No
Vinorelbina	83,8	64,8	88,4	52,4	0,94 (0,67-1,28)	No

Cmax: concentración plasmática máxima alcanzada (ng/ml); SD: sin datos; $Cmax_r$: razón de la Cmax con alimentos y en ayunas.
*Valores de Cmax para alimentos con alto y bajo contenido graso.
CI-1040: inhibidor selectivo de 2 kinasas específicas de la cascada de la Ras-mitogen-activated protein kinase (MAPK); MEK 1 y 2.
Metabolitos de capecitabina: 5'-DFCR (5'desoxi-5-fluorocitidina), 5'-DFUR (5' desoxi-5-fluorouridina), 5-FU (5-fluorouracilo), FUH_2 (dihidro-5-fluorouracilo), FBAL (α-fluoro-β-alanina).
MMI270B: inhibidor de las metaloproteinasas de la matriz extracelular (MMPs), enzimas responsables de la degradación de la matriz extracelular que constituye el tejido conectivo.
S-1: formulación oral de Tegafur (profármaco de 5-fluorouracilo), 5-cloro-2,4-dihidroxipiridina (inhibidor de la dihidropirimidina deshidrogenada o DPD) y ácido oxónico (inhibidor de la fosforibosilación de 5-fluorouracilo en la mucosa intestinal) en proporción molar 1:0,4:1.
SU12662: metabolito activo de Sunitinib.
UFT: fármaco compuesto por Tegafur (FT) y uracilo (1:4). FT es un profármaco de 5-fluorouracilo (5-FU) y uracilo, un inhibidor competitivo y reversible de la enzima Dihidropirimidina deshidrogenasa (DPD), responsable del catabolismo de 5-FU.

Canadiense[23] sobre prácticas de seguridad en nutrición parenteral y enteral ya que no considera las iFA. Se está ante un estado de ignorancia respecto a la importancia clínica de las iFA que se traduce en un retraso en la potencial mejora asistencial de los pacientes en tratamiento con antineoplásicos orales.

En estas poblaciones de pacientes, cambios en el ABC o en las concentraciones plasmáticas en el

Tabla V
Porcentaje de cambio en los valores de referencia para ABC, Cmax y Tmax para los artículos seleccionados y recomendaciones para la administración

Antineoplásico oral	*Alimento*	*Parámetros farmacocinéticos*			*Población de estudio (PK/total)*	*Recomendación para su administración*
	Contenido graso	*ABC (%)*	*Cmax (%)*	*Tmax (h)*		
R-Bicalutamida	Alto	NA	+14	-5	Sanos (15/15)	Administrar con/sin alimentos
S-Bicalutamida		NA	+19	NA		
Capecitabina	Estándar	-50	-250	+1,5	Pacientes (11/11)	Administrar con alimentos
5'-DFCR		-26	-80	+1,5		
5'-DFUR		-15	-53	+1,5		
5-FU		-13	-58	+1,5		
FUH_2		-7	-26	NA		
FBAL		-5	-11	+1		
C-1040	Alto	+400	+460	NA	Pacientes (29/77)	Administrar con alimentos
Erlotinib_DU	Alto	+97	+57	+1,5	Sanos (18/21)	Administrar sin alimentos
DM	Alto	+37	+33	+1,2	Sanos (22/36)	
Exemestano[11]	Alto	+39	+59	+1	Sanos (12/12)	Administrar con o sin alimentos
5-fluorouracilo	Alto	-9	-25	+1-1,5	Pacientes (12/12)	Administrar con/sin alimentos
Gefitinib	Alto	+ 37	+ 32	NA	Sanos (26/96)	Administrar con o sin alimentos
	Alto	-14	-34	+1	Sanos (18/57)	
Indibulina	SD	+15	-17	NA	Pacientes (6/14)	Administrar con alimentos
Irinotecan	Alto	+13	SD	SD	Pacientes (16/25)	Administrar con/sin alimentos
SN-38		+17				
Lapatinib	Alto	+400	+300	+2	Pacientes (27/27)	Administrar sin alimentos
	Bajo	+270	+250	NA		
Letrozol	Estándar	-9%	-23%	+1	Sanos (12/12)	Administrar con o sin alimentos
Lonafarnib_DU	Alto	-23	-50	-5	Sanos (12/12)	Administrar con o sin alimentos
DM	Alto	NA	NA	NA	Pacientes (19/19)	Administrar con alimentos
MM1270B	Ligero	-10	-40	NA	Pacientes (17/17)	Administrar con o sin alimentos
S-1	Alto				Pacientes (18/18)	Administrar con/sin alimentos
Tegafur		NA	-60	+1,5		
Uracil		+12	+11	-1		
5-Fluorouracil		-20	-10	+1		
CDHP		-14	-30	+1		
Ácido Oxonico		-230	-240	+0,5		
Sunitinib[6]	Alto	+18	+10	NA	Sanos (16/16)	Administrar con o sin alimentos
SU12662		-5	-21	2		
Talidomida	Alto	- 5,5	+10	+0,5-1,5	Sanos (13/13)	Administrar con o sin alimentos
Topotecan	Alto	NA	NA	+1	Pacientes (18/18)	Administrar con/sin alimentos
UFT	Alto	–	–	–	(Pacientes 25/25)	Administrar sin alimentos
Tegafur		NA	-34	+2		
Uracilo		-37	-76	+1		
5-fluorouracilo		-37	-76	+1,5		
Vinorelbina[10]	Estándar	-16	NA	+1	Pacientes (12/12)	Administrar con/sin alimentos

PK/total: población de pacientes con datos farmacocinéticos referentes a ABC y Cmax frente a pacientes totales incluidos en el estudio.
Contenido graso estándar: menos del 50% del contenido calórico total procede de las grasas.
NA: no afecta la biodisponibilidad del fármaco, SD: sin datos, ABC: área bajo la curva de concentración plasmática-tiempo, Cmax: concentración plasmática máxima alcanzada, Tmax: tiempo en que se alcanza la concentración plasmática máxima (h). Sin alimentos: 1 h antes o 2 h después de la ingesta.
Metabolitos de capecitabina: 5'-DFCR (5'desoxi-5-fluorocitidina), 5'-DFUR (5' desoxi-5-fluorouridina), 5-FU (5-fluorouracilo), FUH_2 (dihidro-5-fluorouracilo), FBAL (α-fluoro-β-alanina).
CI-1040: inhibidor selectivo de 2 kinasas específicas de la cascada de la Ras-mitogen-activated protein kinase (MAPK); MEK 1 y 2.
SN-38: metabolito activo de Irinotecan
MMI270B: inhibidor de las metaloproteinasas de la matriz extracelular (MMPs), enzimas responsables de la degradación de la matriz extracelular que constituye el tejido conectivo.
S-1: formulación oral de Tegafur (profármaco de 5-fluorouracilo), 5-cloro-2,4-dihidroxipiridina (inhibidor de la dihidropirimidina deshidrogenada o DPD) y ácido oxónico (inhibidor de la fosforibosilación de 5-fluorouracilo en la mucosa intestinal) en proporción molar 1:0,4:1.
SU12662: metabolito activo de Sunitinib.
UFT: fármaco compuesto por Tegafur (FT) y uracilo (1:4). FT es un profármaco de 5-fluorouracilo (5-FU) y uracilo, un inhibidor competitivo y reversible de la enzima Dihidropirimidina deshidrogenasa (DPD), responsable del catabolismo de 5-FU.

Tabla VI

Artículos revisados sin disponibilidad del resultado de bioequivalencia. No disponen del IC 90% de la razón de los valores ABC y Cmax en las dos condiciones estudiadas (con alimentos y sin alimentos). Los datos que se manejan son el tipo de alimento y el porcentaje de cambio en los valores de referencia para ABC, Cmax y Tmax

Referencia	*Antineoplásico oral*	*Alimento*	*Parámetros farmacocinéticos*			*Tipo de población y número (PK/total)*
		Contenido graso	*ABC (%)*	*Cmax (%)*	*Tmax (h)*	
Rugo y cols., 2005[41]	**AG-013736**	Alto	-48	-79	+1	Pacientes (9/36)
Berlin y cols., 2002[xlii]	**Carboxiamidotriazol**	Alto	+29	SD	SD	Pacientes (17/52)
Albertioni y cols., 1993[xliii]	**CdA** (2-cloro-2-deoxiadenosina)	Estándar	NA	-40	+0,8	Pacientes (4/4)
Ehrsson y cols., 1984[xliv]	**Clorambucilo** Acido fenilacético	Estándar	NA NA	-60 NA	+1 +1,5	Pacientes (5/5)
Calvo y cols., 2004[xlv]	**CI-1033**	Alto	NA	NA	+1,3	Pacientes (6/24)
Gunnarson y cols., 1990[xlvi]	**Estramustina** Estrona	Estándar	-67 -56	-57 -46	+2 +2	Pacientes (6/6)
Oscier y cols., 2001[xlvii]	**Fludarabina**	Alto	+7	-10	+1	Pacientes(16/22)
Swaisland y cols., 2001[xlviii]	**Gefitinib**	Alto	-14	-34	+1	Sanos (18/57)
Peng y cols., 2005[xlix]	**Imatinib**	Alto	- 7,4	- 11	+ 1,5	Pacientes(10/10)
Reece y cols., 1986[l] Bosanquet y cols., 1984[li]	**Melfalan**	Estándar Estándar	-39 -220	SD -300	SD +1,5	Pacientes (15/15) Pacientes (5/5)
Tanaka y cols., 2006[lii]	**Nilotinib**	Alto	+82	SD	SD	Sanos (92/92)
Zamboni y cols., 2006[liii]	**9-Nitrocamptotecina** 9-Aminonitrocamptotecina	Estándar	-50 NA	-200 -10	+1,5 -1	Pacientes (16/16)
Hughes y cols., 1999[liv]	**Nolatrexed**	Estándar	NA	-80	+2,25	Pacientes (16/48)
Hoekstra y cols., 2005[lv]	**PKI166**	Alto	NA	NA	+1	Pacientes (10/54)
Rubin y cols., 2006[lvi]	**Vorinostat**	Alto	+38	NA	+2,5	Pacientes (23/23)

Población PK/total: población de pacientes con datos farmacocinéticos referentes a ABC y Cmax frente a pacientes totales incluidos en el estudio.
Contenido graso estándar: menos del 50% del contenido calórico total procede de las grasas.
NA: no afecta la biodisponibilidad del fármaco, SD: sin datos. ABC: área bajo la curva de concentración plasmática-tiempo, Cmax: concentración plasmática máxima alcanzada.
AG-013736: inhibidor del receptor tirosin kinasa del factor de crecimiento del endotelio vascular, factor de crecimiento derivado de las plaquetas y c-kit en pacientes con tumores avanzados.
CI-1033: inhibidor irreversible de la enzima Pan-erbB tirosin kinasa.
PKI166: inhibidor del receptor tirosin kinasa del factor de crecimiento epidérmico.

ámbito de ± 10% pueden llegar a modificar la efectividad y seguridad del tratamiento. Sin embargo, como manifiestan algunos autores recogidos en esta revisión[8,52], incrementos sustanciales en el ABC al administrar estos fármacos con alimentos, pueden no traducirse en modificaciones en la respuesta clínica. Así, para Exemestano, a pesar de observar incrementos del 39% en el ABC en presencia de alimentos, se garantiza el C_{50} o concentración inhibitoria estrogénica y por tanto la respuesta en el paciente. Lo mismo ocurre con Nilotinib, que a pesar de su absorción saturable y por tanto variable, las dosis establecidas garantizan concentraciones plasmáticas superiores al C_{50}, necesarias para inhibir la fosforilación celular de BCR-ABL.

A pesar de las observaciones establecidas para Exemestano y Nilotinib, sería necesario estudiar la relación concentración-eficacia/seguridad para evaluar el alcance clínico de los resultados farmacocinéticos obtenidos, tal y como se apunta en el estudio de Capecitabina[31] De hecho, otros autores demuestran que reducciones en los valores de los parámetros farmacocinéticos básicos, en presencia de alimentos, pueden llegar a disminuir la efectividad del tratamiento; esto sucede para el UFT (tegafur/uracil/fluorouracil) con Leucovorin cuya administración con alimentos reduce

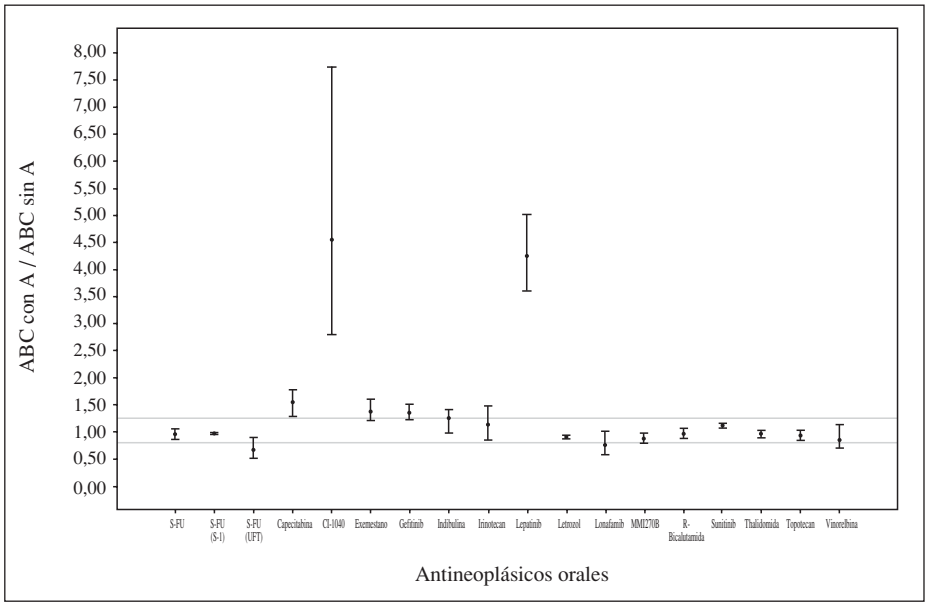

Fig. 1.—IC 90% de la razón de ABC medio, en presencia y ausencia de alimentos.

un 37% la exposición sistémica a 5-Fluorouracil, disminuyendo su actividad antitumoral[34].

Las situaciones descritas demuestran que establecer un procedimiento normalizado para abordar las iFA no es tarea fácil porque los cambios en los parámetros farmacocinéticos básicos por iFA, no parecen relacionarse de forma universal con cambios idénticos en la respuesta clínica en los pacientes. La gran variabilidad interindividual del ABC, de hasta el 200% en el caso de gefitinib, exige evaluar cada paciente y considerar la influencia de la iFA en el ámbito terapéutico del fármaco implicado y la magnitud de la respuesta en términos de potencialidad de fracaso terapéutico en el mismo. Pero esta respuesta, medida a través del perfil de efectos adversos observados[28] no presenta el mismo significado clínico real que en términos de supervivencia en el paciente y por ello, para algunos antineoplásicos orales se concluyen diferentes recomendaciones respecto a su ingesta o no con alimentos, a pesar de que las iFA hayan provocado cambios en el ABC del mismo orden de magnitud[7,36]; es decir, se emiten recomendaciones que anteponen el criterio de tolerancia al criterio de bioequivalencia. Es el caso de vinorelbina[10], que a pesar de la reducción significativa de su biodisponibilidad (18%) en presencia de alimentos de alto contenido graso, al disminuirse la probabilidad de vómitos, prevalece este criterio frente a la reducción potencial de su respuesta. Algo similar ocurre con Lonafarnib[24] en régimen de dosis múltiples, que pese a la situación de bioequivalencia en presencia y ausencia

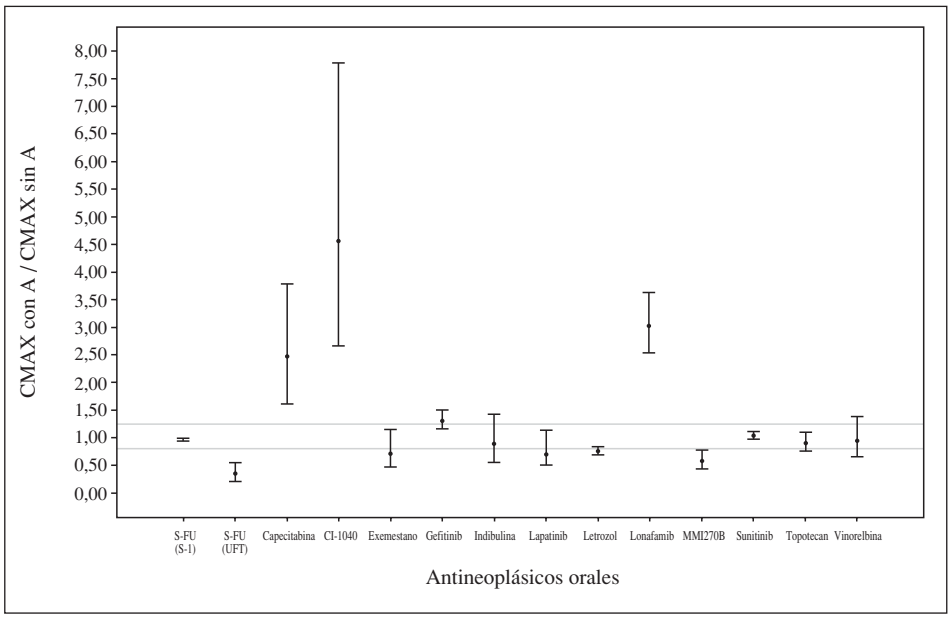

Fig. 2.—IC 90% de la razón de Cmax medio, en presencia y ausencia de alimentos.

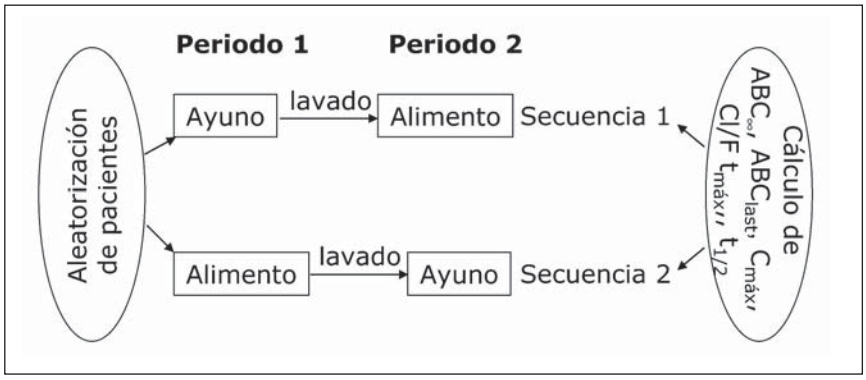

Diagrama 1.—Diagrama de un estudio de bioequivalencia de los fármacos con alimentos.

de alimentos, muestra una mayor incidencia de diarrea y desórdenes metabólicos en condiciones de ayuno (47% *vs* 22%).

La biodisponibilidad de los distintos componentes antineoplásicos formulados en una misma forma de dosificación, es afectada de manera diferente por la presencia o ausencia de alimentos. En este sentido, Godofridus y col[36], estudian el efecto de S-1, una formulación oral de tegafur (profármaco de 5-fluorouracilo), 5-cloro-2,4-dihidroxipiridina (CDHP, inhibidor de la dihidropirimidin deshidrogenada) y ácido oxónico (inhibidor de la fosforibosilación de 5-Fluorouracilo que se acumula en la mucosa gastrointestinal, previniendo la formación de metabolitos tóxicos del mismo) en proporción molar 1:0,4:1. Los autores demuestran que la ingesta del fármaco junto con alimentos afecta únicamente a la farmacocinética del ácido oxónico, pero no a la de tegafur, CDHP y 5-fluorouracilo. En este caso se antepone el criterio de bioequivalencia obtenido al recomendar la administración de esta formulación con alimentos y animando al futuro desarrollo de estudios encaminados a reducir la toxicidad gastrointestinal de estos fármacos.

El estado actual de conocimiento clínico de las iFA sobre los antineoplásicos orales permite destacar que su importancia clínica se identifica y se orienta hacia la seguridad del paciente, dejando en un segundo plano la efectividad del tratamiento en el paciente. Esta percepción profesional, ante el lógico avance de estos tratamientos orales, sus elevados costes mensuales de miles de euros y las potenciales consecuencias clínicas de las iFA, exigen el planteamiento de estudios farmacocinéticos bien diseñados que comparen su biodisponibilidad en ayunas o en presencia de alimentos. Mientras tanto, indicar a los pacientes si deben tomar el medicamento con alimentos, sin alimentos o indistintamente es, para algunos de estos fármacos, inconsistente y de resultado incierto porque la mayoría de las recomendaciones no están basadas en el IC90% de la razón de los valores de ABC y/o Cmax obtenidos con sujetos sanos o pacientes en las dos condiciones estudiadas (con alimentos y sin alimentos).

Anexo I

Deben realizarse en el hombre para disponer de valores de referencia en biodisponibilidad, ya que los datos in vitro (velocidad de disolución) y los obtenidos con modelos animales no se correlacionan con suficiente exactitud.

Deben analizar los efectos de los alimentos sobre la biodisponibilidad del medicamento y su perfil farmacocinético, incluido el correspondiente a metabolitos (en particular con actividad farmacológica) para demostrar que son bioequivalentes la administración con alimentos y en condiciones de ayuno.

Han de correlacionar los efectos de los alimentos sobre la variabilidad de la biodisponibilidad oral y de su respuesta farmacocinética y de eficacia y seguridad para el paciente.

Los estudios han de ser cruzados, en dosis única, con dos periodos y dos tratamientos, en los que el periodo de lavado no sea inferior a cinco semividas biológicas del medicamento implicado (diagrama 1).

- Los sujetos son voluntarios sanos, en número inferior a 50 y a veces realizados sobre un escaso tamaño muestral.
- Los parámetros a cotejar en los sujetos de estudio y para ambas secuencias del mismo son, al menos, Cmax, Tmax, ABC_{∞}, ABC_{last}, $t_{1/2}$ y Cl/F y las variables interindividuales e intraindividuales.
- Finalmente, han de emitir un dictamen de bioequivalencia en ambas condiciones de administración (ayuno y con alimentos).

Referencias

1. Chan LN. Drug-Nutrient Interactions. In Shil (Shils) ME, Shike M, Ross Caballero B, Cousins RJ eds. Modern Nutrition in health and disease. 10th ed. Philadelphia, PA. Lippincott Williams & Wilkins 2006: 1539-1553.
2. Charity D. Scripture and William D. Figg. Drug interactions in cancer therapy. *Nature Rev Cancer* 2006; 6: 546-558.
3. Boutalla JI, Barber JR. A perspective on drug-nutrient interactions. In Boutalla JI, Armenti VA, eds. Handbook of drug-nutrients interactions. Totowa, NJ: Humana Press 2004: 3-25.
4. Santos CA, Boullata JI. An approach to evaluating drug-nutrient interactions. *Pharmacotherapy* 2005; 25 (12): 1789-1800.

5. Zhang L, Strong JM, Oiu W, Lesko LJ, and Huang SM. Scientific Perspectives on drug transporters and their role in drug interactions. *Mol Pharm* 2005; 3 (1): 62-69.
6. Singh BN, Malhotra BK, Effects of food on the clinical pharmacokinetics of anticancer drugs. Underlying mechanism and implications for oral chemotherapy. Clin Pharmacokinet 2004; 43 (15): 1127-1156.
7. Jefferson JW. Drug and diet interactions: avoiding therapeutics paralysis. *J Clin Psychiatric* 1998; 59: 31-39.
8. Couris RR, Tataronis GR, Dallal GE, Blumberg JB, Dwyer JT. Assesment of healthcare professionals' knowledge about warfarin-vitamin k drug-nutrient interactions. *J Am Coll Nutr* 2000; 19 (4): 439-445.
9. Teresa ME, Morgan DE y cols. Attitudes of healthcare professionals toward patient counselling on drug-nutrient interactions. *Ann Pharmacother* 1994; 28: 576-580.
10. Bugat R, Variol P, Roche H, Fumoleau P, Robinet G, Senac I. The effects of food on the pharmacokinetic profile of oral vinorelbine. *Cancer Chemother Pharmacol* 2002; 50: 285-290.
11. Valle M, Di Salle E, Jannuzzo MG, Poggesi I, Rocchetti M, Spinelli R, Verotta D. A predictive model for exemestane pharmacokinetics/pharmacodynamics incorporating the effect of food and formulation. *British Journal of Clinical Pharmacology* 2005; 59 (3): 355-364.
12. Kuppens IE, Witteven PO, Witteveen PO, Schot M, Schuessler VM, Daehling A, Beijnen JH, Voest EE, Schellens JH. Phase I dose- finding and pharmacokinetic trial of orally administered indibulin (D-24851) to patients with solid tumors. *Invest New Drugs* 2007; 25 (3): 227-235.
13. Anderson D, Shelley S, Shelley S, Kellett N, Marshall D, Nimmo W. The Effect of Nateglinide Taken with Food on Gastric Emptying Rates in Healthy Subjects. *Clin Therapeutics* 2003; 25 (6): 1722-1738.
14. Pronsky Z. Food Medications interactions. 14th edition 2006. Birchrunville, PA.
15. Jiménez Torres, NV, Merino San Juan, M, Jiménez Torres NV, Merino Sanjuán M, Ordovás Baines JP, Casabó Alós V. Interacciones entre alimentos y medicamentos: bases farmacoterapéuticas. Primera edición 1999. Ed. Nutricia. Madrid.
16. www.medinteract.net (septiembre 2007).
17. Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products-General considerations. Biopharmaceutics . CDER. FDA. March 2003. USA.
18. De Mario MD, Ratain MJ. Oral chemotherapy: Rationale and future directions. *J Clin Oncol* 1998; 16: 2557-2567.
19. Parsad SD, Ratain MJ. Prescribing oral chemotherapy: *BMJ* 2007; 334: 376.
20. Ratain MJ, Cohen EE. The Value Meal: How to Save 1,700 Per Month or More on Lapatinib. *J Clin Oncol* 2007; 25 (23) (August 10).
21. www.jointcommission.org/Standard (Acceso 30 octubre de 2007).
22. Jain MK, Heyland D, Dhaliwal R, Day AG, Drover J, Keefe L, Gelula M. Dissemination of the Canadian clinical guidelines for nutrition support: results of a cluster randomised controlled trial. *Crit Care Med* 2006; 34 (9): 2362-2369.
23. Seres D, Sacks GS, Pedersen CA, Canada TW, Johnson D, Kumpf V. Parenteral Nutrition Safety Practices: Results of the 2003 American Society for Parenteral and Enteral Nutrition Survey. *J Parenter Enteral Nutr* 2006; 30 (3): 259-265.
24. Zhu Y, Statkevich P, Zhu Y, Statkevich P, Cutler DL. Effect of food on the pharmacokinetics of lonafarnib (SCH 66336) following single and multiple doses. *Int J Clin Pharmacol Ther* 2007; 45 (10): 539-547.
25. Cockshott ID, Oliver SD, Young JJ, Cooper KJ, Jones DC. The effect of food on the pharmacokinetics of the bicalutamide ("Casodex") enantiomers. *Biopharm Drug Dispos* 1997; 18 (6); 499-507.
26. Sioufi A, Sandrenan N, Godbillon J, Trunet P, Czendlik C, Howald H, Pfister Ch, Ezzet F. Comparative bioavailability of letrozol under fed and fasting conditions in 12 healthy subjects after a 2,5mg single oral administration. *Biopharm Drug Dispos* 1997; 18 (6): 489-497.
27. Teo SK, Scheffler MR, Kook KA, Tracewell WG, Colburn WA, Stirling DI, Thomas SD. Effect of a high-fat meal on thalidomide pharmacokinetics and the relative bioavailability of oral formulations in healthy men and women. *Biopharm Drug Dispos* 2000; 21 (1): 33-40.
28. Swaisland H, Smith RP, Laight A, Kerr DJ, Ranson M, Wilder-Smith CH, DuvABChelle T. Single–Dose clinical pharmacokinetic studies of Gefitinib. *Clin Pharmacokinet* 2005; 44 (11): 1165-1177.
29. Bello C, Sherman L, Zhou J, Verkh L, Smeraglia J, Mount J, Klamerus KJ. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects. *Anti-Cancer Drugs* 2006; 17: 353-358.
30. Ling J, Fettner S, Lum B, Riek M, Rakhit A. Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. *Anti-Cancer Drugs* 2008; 19: 209-216.
31. Reigner B, Verweij J, Verweij J, Dirix L, Cassidy J, Twelves C, Allman D, Weidekamm E, Roos B, Banken L, Utoh M, Osterwalder B. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998; 4 (4): 941-948.
32. Herben VMM, Rosing H, Huinink BWW, Van Zomeren DM, Batchelor D, Doyle E, Beusenberg FD, Beijnen JH, Schellens JH. Oral Topotecan: bioavailability and effect food co-administration. *Br J Cancer* 1999; 80 (9): 1380-1386.
33. Eskens FA, Levitt NC, Sparreboom A, Choi Les, Mather R, Verweij J, Harris AL. Effect of Food on the Pharmacokinetics of Oral MMI270B (CGS27023A), a Novel Matrix Metalloproteinase Inhibitor. *Clin Cancer Res* 2000; 6: 431-433.
34. Damle B, Ravandi F, Kaul S, Sonnichsen D, Ferreira I, Brooks D, Stewart D, Alberts D, Pazdur R. Effect of food on the oral bioavailability of UFT and leucovorin in cancer patients. *Clin Cancer Res* 2001; 7 (3): 517-523.
35. Shepard D, Mani S, Shepard DR, Mani S, Kastrissios H, Learned-Coughlin S, Smith D, Ertel P,Magnum S, Janisch L, Fleming GF, Schilsky RL, Ratain MJ. Estimation of the effect of food on the disposition of oral 5-fluorouracil in combination with eniluracil. *Cancer Chemother Pharmacol* 2002; 49 (5): 398-402.
36. Peters GJ, Noordhuis P, Van Groeningen CJ**,** Giacconeg G, Holwerda U, Voorn D, Schrijvers A, Schornagel JH, Beijnen JH, Fumoleau P, Schellens JHM . The Effect of Food on the Pharmacokinetics of S-1 after Single Oral Administration tro Patients with Solid Tumors. *Clin Cancer Res* 2004; 10: 4072-4076.
37. Lorusso PM, Adjei AA, Varterasian M, Gadgeel S, Reid J, Mitchell DY, Hanson L,DeLuca P, Bruzek L, Piens J, Asbury P, Van Becelaere K, Herrera R, Sebolt-Leopold J, Meyer MB. Phase I and pharmacodynamic study of the oral MEK inhibitor CI-1040 in patients with advanced malignancies. *J Clin Oncol* 2005; 23 (23): 5281-5293. Epub 2005 Jul 11.
38. Soepenberg O, Dumez H, Verweij J, de Jong FA, de Jonge MJ, Thomas J, Eskens FA, van Schaik RH, Selleslach J, Ter Steeg J, Lefebvre P, Assadourian S, Sanderink GJ, Sparreboom A, van Oosterom AT. Phase I pharmacokinetic, food effect, and pharmacogenetic study of oral irinotecan given as semisolid matrix capsules in patients with solid tumors. *Clin Cancer Res* 2005; 1 (4): 1504-1511.
39. Kuppens IELM, Witteveen PO, Schot M, Schuessler VM, Daehling A, Beijnen JH, Voest EE, Schellens JHM. Phase I dose-finding and pharmacokinetic trial of orally administered indibulin (D-24851) to patients with solid tumors. *Invest New Drugs* 2007; 25: 227-235.
40. Reddy N, Cohen R, Whitehead B, Kosch K, Stead A, Beelen A, Lewis L. A phase I, open-label, three period, randomized, crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients. *Clin Pharmacokinet Ther* 2007; 81: S16-S17.
41. Rugo HS, Herbst RS, Liu G, Park JW, Kies MS, Steinfeldt HM, Pithavala YK, Reich SD, Freddo JL, Wilding G. Phase I Trial of the Oral Antiangiogenesis Agent AG-013736 in Patients With

Advanced Solid Tumors: Pharmacokinetic and Clinical Results. *J Clin Oncol* 2005; 23 (24): 5474-5483.
42. Berlin J, Tutsch KD, Arzoomanian RZ, Alberti D, Binger K, Feierabend C, Dresen A, Marnocha R, Pluda J, Wilding G. Phase I and pharmacokinetic study of a micronized formulation of carboxyamidotriazole, a calcium signal transduction inhibitor: toxicity, bioavailability and the effect of food. *Clin Cancer Res* 2002; 8 (1): 86-94.
43. Albertioni F, Juliusson G, Liliemark J. On the bioavailability of 2-chloro-2'-deoxyadenosine (CdA). The influence of food and omeprazole. *Eur J Clin Pharmacol* 1993; 44 (6): 579-582.
44. Ehrsson H, Wallin I, Simonsson B, Hartvig P, Oberg G. Effect of food on pharmacokinetics of chlorambucil and its main metabolite, phenylacetic acid mustard. *Eur J Clin Pharmacol* 1984; 27 (1): 111-114.
45. Calvo E, Tolcher AW, Hammond LA, Patnaik A, de Bono JS, Eiseman IA, Olson SC, Lenehan PF, McCreery H, Lorusso P, Rowinsky EK. Administration of CI-1033, an irreversible pan-erbB tyrosine kinase inhibitor, is feasible on a 7-day on, 7-day off schedule: a phase I pharmacokinetic and food effect study. *Clin Cancer Res* 2004; 10 (21): 7112-7120.
46. Gunnarsson PO, Davidsson T, Anderson SB, Backman C, Johansson SA. Impairment of estramustine phosphate absortion by concurrent intake of milk and food. *Eur J Clin Pharmacol* 1990; 38: 189-193.
47. Oscier D, Orchar JA, Culligan D, Cunningham D, Johnson S, Parker A, Klein M, Gieschen H. The bioavailability of oral fludarabine phosphate is unaffected by food. *The Haematology Journal* 2001; 2: 316-321.
48. Swaisland H, Laight A, Stafford L, Jones H, Morris C, Dane A, Yates R. Pharmacokinetics and Tolerability of the Orally Active Selective Epidermal Growth Factor Receptor Tyrosyne Kinase Inhibitor ZD1839 in Healthy Volunteers. *Clin Pharmacokinet* 2001; 40 (4): 297-306.
49. Peng B, Lloyd P, Schran H. Clinical pharmacokinetic of imatinib. *Clin Pharmacokinet* 2005; 44 (9): 879-894.
50. Reece PA, Kotasek D. The effect of food on oral melphalan absorption. *Cancer Chemother Pharmacol* 1986; 16 (2): 194-197.
51. Bosanquet AG, Gilby ED. Comparison of the fed and fasting states on the absorption of melphalan in multiple myeloma. *Cancer Chemother Pharmacol* 1984; 12 (3): 183-186.
52. Tanaka C, Smith T, Kantarjian H, Giles F, Ottmann O, Bhalla K, Grouss K, Sethuraman V, Thomas K, Schran H. Clinical pharmacokinetics (PK) of AMN107, a novel inhibitor of Bcr-Abl, in healthy subjects and patients with imatinib resistant or intolerant chronic myelogenous leukemia (CML) or relapsed/refractory Ph+ acute lymphocytic leukemia (Ph+ALL). JCO, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 3095.
53. Zamboni WC, Goel S, Iqbal T, Parise RA, Strychor S, Repinski TV, Egorin MJ, Mani S. Clinical and pharmacokinetic study evaluating the effect of food on the disposition of 9-nitrocamptothecin and its 9-aminocamptothecin metabolite in patients with solid tumors. *Cancer Chemother Pharmacol* 2006; 57 (5): 631-639.
54. Hughes AN, Rafi I, Griffin MJ, Calvert AH, Newell DR, Calvete JA, Johnston A, Clendeninn N, Boddy AV. Phase I Studies with the Nonclassical Antifolate Nolatrexed Dihydrochloride (AG337, THYMITAQ) Administered Orally for 5 Days. *Clin Cancer Res* 1999; 5: 111-118.
55. Hoekstra R, Dumez H, Eskens FA, Van der Gaast A, Planting AS, de Heus G, Sizer KC, Ravera C, Vaidyanathan S, Bucana C, Fidler IJ, van Oosterom AT, Verweij J. Phase I and pharmacologic study of PKI166, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *Clin Cancer Res* 2005; 11 (19 Pt 1): 6908-6915.
56. Rubin EH, Agrawal NG, Friedman EJ, Scott P, Mazina KE, Sun L, Du L, Ricker JL, Frankel SR, Gottesdiener KM, Wagner JA, Iwamoto M. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* 2006; 12 (23): 7039-7045.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):273-281
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Plant-derived health - the effects of turmeric and curcuminoids

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Abstract

Plants contain numerous polyphenols, which have been shown to reduce inflammation and hereby to increase resistance to disease. Examples of such polyphenols are isothiocyanates in cabbage and broccoli, epigallocatechin in green tee, capsaicin in chili peppers, chalones, rutin and naringenin in apples, resveratrol in red wine and fresh peanuts and curcumin/curcuminoids in turmeric. Most diseases are maintained by a sustained discreet but obvious increased systemic inflammation. Many studies suggest that the effect of treatment can be improved by a combination of restriction in intake of proinflammatory molecules such as advanced glycation end products (AGE), advanced lipoperoxidation end products (ALE), and rich supply of antiinflammatory molecules such as plant polyphenols. To the polyphenols with a bulk of experimental documentation belong the curcuminoid family and especially its main ingredient, curcumin. This review summarizes the present knowledge about these turmeric-derived ingredients, which have proven to be strong antioxidants and inhibitors of cyclooxigenase-2 (COX-2), lipoxygenase (LOX) and nuclear factor κ B (NF-κB) but also AGE. A plethora of clinical effects are reported in various experimental diseases, but clinical studies in humans are few. It is suggested that supply of polyphenols and particularly curcuminoids might be value as complement to pharmaceutical treatment, but also prebiotic treatment, in conditions proven to be rather therapy-resistant such as Crohn's, long-stayed patients in intensive care units, but also in conditions such as cancer, liver cirrhosis, chronic renal disease, chronic obstructive lung disease, diabetes and Alzheimer's disease.

(*Nutr Hosp*. 2009;24:273-281)

Key words: *Diabetes. Alzheimer's disease. Turmeric. Curcuminoids.*

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Recibido: 2-XI-2008.
Aceptado: 6-II-2009.

EFECTOS SALUDABLES DE LA CÚRCUMA Y DE LOS CURCUMINOIDES

Resumen

Las plantas contienen un gran número de sustancias de naturaleza polifenólica con capacidad para reducir los procesos inflamatorios y, por lo tanto, incrementar la resistencia a determinadas enfermedades. Ejemplos de algunos polifenoles son los isotiocianatos presentes en la col y el brócoli, epigalocatequinas del té verde, capsaicina de las guindillas, chalonas, rutina y naringenina de las manzanas, resveratrol del vino tinto y de los cacahuetes, y curcumina y curcuminoides de la cúrcuma. La mayoría de las enfermedades tienen un componente discreto pero obvio de inflamación sistémica. Muchos trabajos han sugerido que los efectos de estos tratamientos podrían ser mejorados tras la restricción de la ingesta de moléculas proinflamatorias, como los productos avanzados de la glicación (AGE) y lipoperoxidación (ALE), junto con la suplementación de moléculas antiinflamatorias, como algunos polifenoles obtenidos de las plantas. Concretamente, los efectos de los curcuminoides y de su principal componente, la curcumina, han sido ampliamente documentados. Esta revisión, recopila los datos actuales acerca de las principales moléculas activas derivadas de la cúrcuma, para las cuales se ha demostrado que poseen una potente actividad antioxidante, inhiben la ciclooxigenasa 1 (COX-1), la lipoperoxidasa (LPO), el factor nuclear NF-κB (NF-κB), así como los AGE. La mayoría de los efectos han sido demostrados mediante estudios experimentales; sin embargo, los estudios clínicos en humanos son escasos. Se ha sugerido que la suplementación con curcuminoides podría ser interesante como un complemento para los tratamientos farmacológicos, además de cómo tratamiento prebiótico en condiciones en las que no existe una terapia eficaz, como en el caso de la enfermedad de Crohn, en pacientes ingresados en Unidades de Cuidados Intensivos durante periodos prolongados, y también en patologías tales como el cáncer, la cirrosis hepática, la enfermedad renal crónica, la enfermedad digestiva obstructiva, la diabetes y la enfermedad de Alzheimer. (Full spanish translation in www.nutricionhospitalaria.com).

(*Nutr Hosp*. 2009;24:273-281)

Palabras clave: *Diabetes. Alzheimer. Cúrcuma. Curcuminoides.*

Introduction

Modern medicine has to a large extent failed in its ambition to control both acute and chronic diseases. Acute diseases have an unacceptably high morbidity and co-morbidity. Furthermore, the world suffers an epidemy of chronic diseases of a dimension never seen before, and these diseases are now like a prairie fire also spreading to so called developing countries. Chronic diseases —including diseases such as cardiovascular and neurodegenerative conditions, diabetes, stroke, cancers and respiratory diseases— constitute today 46% of the global disease burden and 59% of the global deaths; each year on earth approximately 35 million individuals will die in conditions related to chronic diseases, and the numbers are increasing and have done so for several years.[1] Similarly, the morbidity related to advanced medical and surgical treatments and emergencies, especially infectious complications, is also fast increasing; sepsis is the most common medical and surgical complication.

Accumulating evidence supports the association of chronic diseases (ChDs) to modern life style: stress, lack of exercise, abuse of tobacco and alcohol, and to the transition from natural unprocessed foods to processed, calorie-condensed and heat-treated foods. There is a strong association between ChD and reduced intake of plant fibres, plant antioxidants and increased consumption of industrially produced and processed dairy products, refined sugars and starch products. Heating up milk (pasteurization), and especially production of and storage of milk powder, produces large amounts of advanced glycation products (AGEs) and advanced lipoxidation products (ALEs), known as potent inducers of inflammation.[2] This information is especially important as many foods such as ice cream, enteral nutrition solutions and baby formulas are based on milk powder and its derivatives. Bread, especially from gluten-containing grains, is also rich in molecules with documented pro-inflammatory effects, and bread crusts often used experimentally to induce inflammation.[3-5]

Plant consumption-derived protection

Common to those suffering ChD as well as critical illness (CI) is that they suffer an increased degree of inflammation, most likely due to their Western lifestyle. We are increasingly aware that plant-derived substances, often referred to as chemopreventive agents, have an important role to play in control of inflammation. These substances are not only inexpensive, they are also easy available, and have no or limited toxicity. Among these numerous chemo-preventive agents are a whole series of phenolic and other compounds believed to reduced speed of aging and prevent degenerative malfunctions of organs. For these reasons, the interest for the study of these compounds has increased in the last years. Among them, various curcuminoids found in turmeric curry foods and thousands more of hitherto less or unexplored substances have received an increasing attention for their strong chemo-preventive ability in recent few years. Curcumin is the most explored of the so called curminoids, a family of chemopreventive substances present in the spice turmeric. Although the substance has been known for some time, it is in the most recent years that the interest has exploded, much in parallel with increasing concern for severe side-effects of synthetic cyclooxigenase-2 (COX-2) inhibitors, marketed by pharmaceutical industry. This review reported mainly curcumin experimental and clinical studies focus on curcumin and its effects (table I).

Table I
Curcuminoid main effects

	Main mechanisms of action
Atherosclerosis	↓ LDL oxidation[29,31]; Cell membrane stabilisation[30]; ↑ antioxidant plasma concentrations[31]
Cancer	Induces apoptosis[36-45]; Inhibits metastasis[46]
Diabetes	↓ glucose, haemoglobin and glycated haemoglobin[48]; ↑ antioxidant protection[48]
Gastric diseases	↓ growth of some *Helicobacter* strains[49]; ↓ NF-κB and mitogenic response [50]; Antifungic properties[51]
Hepatic diseases	↓ lipid accumulation[52-54]; ↓ hepatic risk biomarkers[53,55]; ↓ NF-κB-dependent gene expression; ↓ inflammatory molecules expression[55,56]; ↓ oxidation[55]
Pancreatic diseases	↓ NF-κB activation and activator protein 1 expression; ↓ inflammatory molecules expression[57]; ↓ caspase-3 activation[57]; ↓ intra-pancreatic trypsin activation[57]
Intestinal diseases	↓ lipid peroxidation[58]; ↓ NF-κB activation[58,60]; ↓ nitric oxide levels[58]; immune function regulation[58]; ↓ MAPK p38[59]; ↓ inflammatory response[59,60]
Neurodegenerative diseases	Free radical scavenger[66, 67]; ↓ oxidative markers[70]; ↓ β-amyloid deposits [69]
Ocular diseases	Antioxidant activity[77-79]
Respiratory diseases	↓ fibrogenesis[80]; inflammatory markers[80]; calcium and chloride pump alteration[82,83]; Anti-asthmatic effect[84]
Tobacco smoke-induced injury	↓ NF-κB activation:↓ anti-inflammatory molecules[85]

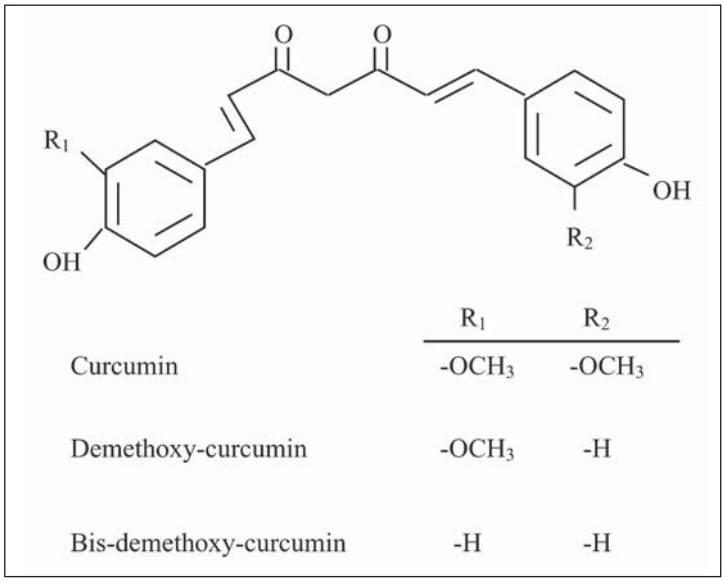

Fig. 1.—Structure of curcumin and its main derivatives.

Turmeric – approved as food additive

Curcumin, 1,7-bis (4-hydroxy-3-methoxyphenol)-1,6heptadiene-3,5-dione), or dipheruloylquinone (fig. 1), is the most abundant polyphenol present in the dietary spice turmeric and received from dried rhizozomes of the perennial herb *Curcuma longa* Linn, a member of the ginger family. Turmeric is mainly known for its excellent ability to preserve food, and is approved as food additive in most Western countries. It is produced in several Asian and South-American countries. Only in India are about 500,000 metric tonnes produced each year, of which about half is exported. It has, in addition to extensive use as food additive, for generations also been used in traditional medicine for treatment of various external or internal inflammatory conditions such as arthritis, colitis and hepatitis.

The molecule of curcumin resembles ubiquinols and other phenols known to possess strong antioxidant activities. Its bioavailability on oral supplementation is low, but can be improved by dissolution in ambivalent solvents (glycerol, ethanol, DMSO).[6] It is also reported to be dramatically elevated by co-ingestion of peperine (a component of pepper), demonstrated both in experimental animals and humans.[7] Polyphenols, isothiocyanates such as curcumin and flavonoids such as resveratrol, are all made accessible for absorption into the intestinal epithelial cells and the rest of the body by digestion/fermentation in the intestine by microbial flora.[8] Several studies has demonstrated that curcumin is atoxic, also in very high doses.[9-10] It is estimated that adult Indians consume daily 80-200 mg curcumin per day.[11] A common therapeutic dose is 400-600 mg curcumin three times daily corresponding to up to 60 g fresh turmeric root or about 15 g turmeric powder, since the content of curcumin in turmeric is usually 4-5%. Finally, it is noteworthy to mention that the treatment of humans during three months with 8,000 mg curcumin per day showed no side effects.[10]

Curcumin – an antioxidant and inhibitor of NF-κB, COX-2, LOX and iNOS and against stress-induced overinflammation

NF-κB plays a critical role in several signal transduction pathways involved in chronic inflammatory diseases[12] such as asthma and arthritis and various cancers.[13] Activation of NF-κB is linked with apoptotic cell death; either promoting or inhibiting apoptosis, depending on cell type and condition. The expression of several genes such as COX-2, lipoxygenase (LOX), matrix mettaloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), interleukin-8 (IL-8), eotaxin, cell surface adhesion molecules and anti-apoptotic proteins are regulated by NF-κB.[14] COX-2 is inducible and barely detectable under normal physiological conditions, but is rapidly, but transiently, induced as an early response to proinflammatory mediators and mitogenic stimuli including cytokines, endotoxins, growth factors, oncogenes and phorbol esters. COX-2 synthesizes series-2 prostaglandins (PGE_2, PGF_2-α), which contribute to inflammation, swelling and pain. PGE_2 promotes production of IL-10, a potent immuno-suppressive cytokine produced especially by lymphocytes and macrophages, and suppression of IL-12.[15] Inducible nitric oxide synthase (iNOS), activated by NF-κB, is another enzyme that plays pivotal role in mediating, inflammation, especially as it acts in synergy COX-2.

Curcumin is not only an inexpensive atoxic and potent COX-2 and iNOS inhibitor,[16] it is also a potent inducer of heat shock proteins (HSPs) and potential cytoprotector.[17,18] Curcumin does not only inhibit

COX-2, it also inhibits lipooxygenases (LOX) and leukotreines such as LBT_4 and 5-hydroxieicosenoic (5-HETE),[19] especially when bound to phosphatidylcholine micelles.[20] It is also reported to inhibit cytochrome P450 isoenzymes and thereby activation of carcinogens.[21] Curcumin has the ability to intercept and neutralize potent prooxidants and carcinogens, both ROS (superoxide, peroxyl, hydroxyl radicals) and NOS (nitric oxide —NO—, peroxynitrite).[22] It is also a potent inhibitor of tissue growth factor beta (TGF-β) and fibrogenesis,[23] which is one of the reasons, why it can be expected to have positive effects in diseases such as kidney fibrosis, lung fibrosis, liver cirrhosis and Crohn's Disease and in prevention of formation of tissue adhesions.[24] Finally, curcumin is suggested to be especially effective in Th1-mediated immune diseases as it effectively inhibits Th1 cytokine profile in $CD4^+$ T cells by interleukin-12 production.[25]

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another, and interactions between herbs and drugs, even if structurally un-related, may increase or decrease the pharmacological and toxicological effects of either component.[26,27] It is suggested that curcumin may increase the bioavailability of vitamins such as vitamin E and also decrease cholesterol, as curcumin in experimental studies significantly raises the concentration of α-tocopherol in lung tissues and decreases plasma cholesterol.[28]

Curcumin in acute and chronic diseases

Atherosclerosis: Oxidation of low density lipoproteins (LDL) is suggested to play a pivotal role in the development of arteriosclerosis, and LDL oxidation products are toxic to various types of cells including endothelial cells. Curcumin has a strong capacity to prevent lipid peroxidation, stabilize cellular membranes, inhibit proliferation of vascular smooth muscle cells, and inhibit platelet aggregation; all important ingredients in the pathogenesis of arteriosclerosis. Curcumin was found to be the most effective, when the ability to inhibit the initiation and propagation phases of LDL oxidation were compared with a defined antioxidant butylated hydroxy anisole (BHA), capsaisin, quercetin.[29] Supply of curcumin, but also capsaicin and garlic (allecin) to rats fed of a cholesterol-enriched diet prevented both increase in membrane cholesterol and increased fragility of the erythrocytes.[30] Significant prevention of early atherosclerotic lesions in thoracic and abdominal aorta are observed in rabbits fed an atherogenic diet for thirty days, accompanied by significant increases in plasma concentrations of coenzyme Q, retinol and α-tocopherol and reductions in LDL conjugated dienes and in thiobarbituric acid-reactive substances (TBARS), an expression of ongoing oxidation.[31]

Cancer: Cancer is a group of more than 100 different diseases, which manifest itself in uncontrolled cellular reproduction, tissue invasion and distant metastases.[32] Behind the development of these diseases are most often exposure to carcinogens, which produce genetic damage and irreversible mutations, if not repaired. During the last fifty years attempts have been made to find or produce substances that could prevent these processes, so called chemopreventive agents. Cancers are generally less frequent in the developing world, which has been associated both with less exposure to environmental carcinogens and to a richer supply of natural chemopreventive agents. The incidence per 100,000 population is in the USA considerably higher for the following diseases compared to India: prostatic cancer (23 X), melanoma skin cancer (male 14 X, female 9 X), colorectal cancer (male 11 X, female 10 X), endometrial cancer (9 X), lung cancer (male 7 X, female 17 X), bladder cancer (male 7 X, female 8 X) breast cancer (5 X), renal cancer (male 9 X, female 12 X).[35] These differences are for some diseases such as breast cancer and prostatic cancer even greater when compared to China.

The consumption of saturated fat and sugary foods is much less in the Asian countries, but equally important, the consumption of plants with high content of chemopreventive substances is significantly higher in these countries. As an example, the consumption of curcumin has for centuries been about 100 mg/day in these Asian countries.[34] Curcumin induces *in vitro* apoptosis of various tumour cell lines: breast cancer cells,[34,35] lung cancer cells,[36] human melanoma cells,[37] human myeloma cells,[38] human leukemia cell lines,[39] human neuroblastoma cells,[40] oral cancer cells,[41] prostatic cancer cells.[42-45] Curcumin has, in experimental models also demonstrated ability to inhibit intrahepatic metastases.[46] Few in vivo experimental studies and no clinical controlled trials are this far concluded. However, a recent phase I study reported histologic improvement of precancerous lesions in 1 out of 2 patients with recently resected bladder cancer, 2 out of 7 patients of oral leucoplakia, 1 out of 6 patients of intestinal metaplasia of the stomach, and 2 out of 6 patients with Bowen's disease.[47] However, the main purpose of the study was to document that curcumin is not toxic to humans when taken by mouth for 3 months in a dose of up to 8 mg/day.

Diabetes: Turmeric (1 g/kg body weight) or curcumin (0.08 g/kg body weight) were in a recent study supplied daily for three weeks to rats with alloxan-induced diabetes and compared to controls.[48] Significant improvements were observed in blood glucose, hemoglobin and glycosylated hemoglobin as well than in plasma and liver TBARS and glutathione. On the other hand, it was also observed that the activity of sorbitol dehydrogenase (SDH), which catalyzes the conversion of sorbitol to fructose, was significantly lowered by treatment both with turmeric and curcumin.

Gastric diseases: When the in vitro effects against 19 different *Helicobacter pylori* strains, including five cagA+ strains (cag A is the strain-specific *H pylori* gene linked to premalignant and malignant lesions)

were studied, both treatments were found to be equally effective as both treatments did significantly reduce growth of all the strains studied.[49] Subsequent studies did also demonstrate that curcumin inhibits infection and inflammation of gastric mucosal cells through the inhibition of activation of NF-κB, degradation of IκBα, NF-κB DNA binding and the activity of IκB kinases α and β. No curcumin-induced effects were observed on mitogen-activated protein kinases (MAPK), extracellular signal regulating kinases 1/2 (ERK1/2) and p38. *H pylori*-induced mitogenic response was completely blocked by curcumin.[50] Significant antifungal properties against various fungal, especially phytopathogenic, organisms by curcumin are also reported.[51]

Hepatic diseases: Dietary supply of curcuminoids is also reported to increase hepatic acyl-CoA and prevent high-fat diet-induced accumulation in the liver and adipose tissues in rats.[54] Ethanol-induced steatosis is known to be further aggravated by supply of polyunsaturated fatty acids (PUFA)-rich vegetable oils, which has been thermally oxidized. Rats gavaged for 45 days with a diet containing 20% ethanol and 15 % sunflower oil, heated to 180 °C for 30 min, showed extensive histopathological changes with focal and feathery degeneration, micronecroses and extensive steatosis in the liver and extensive inflammation vessel congestion and fatty infiltration in the kidneys, changes, which largely could be prevented by simultaneous supply of curcumin or particularly photo-irradiated curcumin, e.g. curcumin kept in bright sunshine for five hours.[53] Both products were supplied in a dose of 80 mg/kg body weight. Both products did significantly inhibit elevations in alkaline phasphatases (ALP) and γ-glutamyl transferase (γGT). Similar beneficial effects were observed on histology in various tissues and in hepatic content of cholesterol, triglycerides free fatty acids and phospholipids.[53] Rats were, in another study for four weeks, fed with fish oil and ethanol which resulted in hepatic lesions consisting in fatty liver, necrosis and inflammation. Supply of curcumin in a daily dose of 75 mg/kg body weight to these rats prevented the histological lesions.[54] Curcumin was observed to in part to suppress NF-κB-dependent genes, to block endotoxin-mediated activation of NF-κB and to suppress the expression of cytokines, chemokines, COX-2 and iNOS in Kupffer cells. Similar effects were also observed in carbon tetrachloride (CCl_4)-induced injuries. Pretreatment during four days with curcumin (100 mg/kg body weight) before intraperitoneal injection of CCl_4 prevented significantly subsequent increases in TBARS, alanine aminotransferase (ALT) and aspertate aminotransferase (AST) and in hydroxyproline (μg/g liver tissue).[55] A recent study has shown that curcumin administration prevent the reduction of cytochrome enzyme P450 expression induced in inflammatory situations.[56]

Pancreatic diseases: The effect of curcumin to reduce the damage to pancreas was studied in two different models; cerulein-induced and ethanol and colecistokinin (CCK)-induced pancreatitis.[57] Curcumin was administered intravenously in parallel with induction of pancreatitis; a total of 200 mg/kg body weight was administered during the treatment period of six hours. Curcumin treatment reduced significantly histological injuries, the acinar cell vacuolization and neutrophil infiltration of the pancreatic tissue, the intrapancreatic activation of trypsin, the hyperamylasemia and hyperlipasemia, and the pancreatic activation of NF-κB, IκB degradation, activation of activator protein (AP)-1and various inflammatory molecules such as IL-6, TNF-α, chemokine KC, iNOS and acidic ribosomal phosphoprotein (ARP). Curcumin did in both models also significantly stimulate pancreatic activation of caspase-3.[57]

Intestinal diseases: Pretreatment during 10 days with curcumin in a daily dose of 50 mg/kg body weight before induction of trinitrobenzene sulphonic acid (TNBS) colitis resulted in a significant reduction in degree of histological tissue injury, neutrophil infiltration (measured as decrease in myeloperoxidase activity) and lipid peroxidation (measured as decrease in malondialdehyde activity) in the inflamed colon, as well as in a decreased serine protease activity.[58] A significant reduction in NF-κB activation and reduced levels of NO, superoxide anion and a regulation of the immune function were also found. Specifically, a marked suppression of Th1 functions, through a lower expression of interferon gamma (IFNγ) mRNA and a better Th2 protective expression improved colonic mucosa induced damage.[58] In another similarly designed study curcumin was added to the diet during 24 h before and 2 wk after the induction of TNBS colitis. A significant reduction in COX-2 and iNOS expression could be attributed to the lower activation of MAPK p38.[59] Indeed, curcumin modulates proinflammatory cytokines expression, attenuating IL-1β TNBS-induced damage, and increase IL-10 expression.[60] Curcumin was also supplied in combination with caffeic acid phenethyl ester to animals treated with cytostatic drugs (arabinose cytosine and methotrexate). The treatment did not only inhibit the NF-κB induced mucosal barrier injury but was also shown to increase the *in vitro* susceptibility of the non-transformed small intestinal rat epithelial cell to the cytostatic agents.[61] However, a recent study has shown that the effect of curcumin of TNBS-induced damage on intestinal mucosa depend on the experimental model. These authors concluded that the therapeutic value of curcumin depends on the nature of the immune alteration during intestinal bowel disease.[62]

Neurodegenerative diseases: A growing body of evidence implicates free radical toxicity, radical induced mutations and oxidative enzyme impairment and mitochondrial dysfunction in neurodegenerative diseases (NDD). Significant oxidative damage is observed in all NDD, which in the case of Alzheimer disease (AD) leads to extracellular deposition of β-amyloid (Aβ) as senile plaques.

Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen has proven effective to prevent progress of AD in animal models,[63] but gastrointestinal and occasional liver and kidney toxicity induced by inhibition of COX-1 precludes widespread chronic use of the drug.[64] Use of antioxidants such as vitamin E (α-tocopherol) has proven rather unsuccessful even when high doses were used.[65] Vitamin E, α-tocopherol, is in contrast to γ-tocopherol a poor scavenger of NO-based free radicals. However, Curcumin is a several times more potent scavenger than vitamin E,[66] and in addition also a specific scavenger of NO-based radicals.[67] When tried in a transgenic mouse model of AD a modest dose (24 mg/kg body weight), but not a > 30 times higher dose (750 mg/kg body weight) of curcumin did significantly reduce oxidative damage and amyloid pathology.[68] Similar observations, reductions in both Aβ deposits and in memory deficits are also made in Sprague Dawley rats.[69] The age-adjusted prevalence of both AD[70] and Parkinson's disease[71] is in India, with its significantly higher intake of turmeric, much lower than in Western countries, especially the USA. However, the preventive effects of consumption of turmeric can also be achieved with other polyphenol-rich fruits and vegetables if consumed in enough quantities. Blueberries, strawberries and spinach in doses of 18.6, 14.8 and 9.1 g of dried extract/kg body weight were demonstrated effective in reversing age-related deficits in both neuronal and behavioural parameters.[72] A study from 1999 is of special interest. Rats on chronic ethanol supply were randomized to 80 mg/kg body weight of curcumin or control and compared to non-intoxicated normal rats.[73] The degree of histopathological changes and levels of TBARS, cholesterol, phospholipids, and free fatty acids in brain tissue were significantly improved after curcumin treatment.

Ocular diseases: Cataract, an opacity of the eye lens, is the leading cause of blindness worldwide, responsible for blindness of almost 20 million in the world.[74] Nutritional deficiencies, especially lack of consumption of enough antioxidants, diabetes, excessive sunlight, smoking and other environmental factors are known to increase the risk of cataracts.[75] However, the age-adjusted prevalence of cataract in India is, however, three times that of the United States,[76] despite that have three different experimental studies reported significant preventive effects of curcumin against cataracts induced by naphthalene,[77] galactose,[78] and selenium.[79]

Respiratory diseases: As mentioned above, curcumin is a potent inhibitor of TGF-α and fibrogenesis,[24] and suggested to have positive effects in fibrotic diseases in kidneys, liver, intestine (Crohn's Disease), body cavities (prevention of fibrous adhesions)[18] and on conditions with lung fibrosis,[80] including cystic fibrosis. The latter is of special interest as it has been especially linked to glutathione deficiency. The effect of curcumin against amiodarone-induced lung fibrosis was recently studied in rats.[80] Significant inhibition of lactate dehydrogenase (LDH) activity, infiltration of neutrophils, eosinophils and macrophages in lung tissue, lipopolysaccharide (LPS)-stimulated TNF-α release, phorbole myristate acetate (PMA)-stimulated superoxide generation, myeloperoxidase (MPO) activity, TGF-β1 activity, lung hydroxyproline content and expression of type I collagen and c-Jun protein were observed when curcumin was supplemented in a dosis of 200 mg/kg body weight in parallel with intratracheal instillation of 6.25 mg/kg body weight of amiodarone.[80]

Curcumin exhibits structural similarities to isoflavonoid compounds that seem to bind directly to the CFTR protein and alter its channel properties.[79] Egan et al,[80] who had previously observed that curcumin inhibits a calcium pump in endoplasmic reticulum, thought that reducing the calcium levels might liberate the mutant Cystic fibrosis transmembrane conductance regulator (CFTR) and increase its odds of reaching the cell surface- see also.[81] Previously, Egan et al observed that curcumin inhibits endoplasmic reticulum calcium bomb and proposed that calcium reduction may release a mutated CFTR that is able to reach cell surface.[82] The ΔF508 mutation, the most common cause of cystic fibrosis, will induce a misprocess in the endoplasmatic reticulum of a mutant CFTR gene. A dramatic increase in survival rate and in normal cAMP-mediated chloride transport across nasal and gastrointestinal epithelia was observed in gene-targeted mice homozygous for the ΔF508 when supplemented curcumin.[83] No human studies are yet reported and it is too early to know if this treatment will be able to halt or reverse the decline in lung function also in patients with cystic fibrosis. An eventual anti-asthmatic effect of curcumin was recently tested in guinea-pigs sensitized with ovalbumin and significant reductions observed both in airway constriction and in airway hyperreactivity to histamine.[84]

Tobacco/cigarette smoke-induced injuries: Cigarette smoke is suggested to cause 20% of all deaths and ~30% of all deaths from cancer. This smoke contains thousands of compounds of which about hundred are known carcinogens, co-carcinogens, mutagens and/or tumor promoters. Each puff of smoke contains over 10 trillion free radicals. Antioxidant levels in blood are also significantly reduced in smokers. Activation of NF-κB has been implicated in chemical carcinogenesis and tumorigenesis through activation of several genes such as COX-2, iNOS, MMP-9, IL-8, cell surface adhesion molecules, anti-apoptotic protein and others. A recent study reports that curcumin abrogates the activation of NF-κB, which correlates with down-regulation of COX-2, MMP-9 and cyclin D1 in human lung epithelial cells.[85]

Plant antioxidants - released by gastrointestinal microbiota

All chronic diseases are in a way related, they develop all as a result of a prolonged and exaggerated

inflammation.[86] Their development can most likely be prevented or at least delayed by extensive consumption of antioxidants such as curcumin. It is important to remember, that it is almost exclusively through microbial fermentation of the different plants that bioactive antioxidants are released and absorbed. Clearly flora and supplied lactic acid bacteria/probiotics play an important role. It is therefore unfortunate that both size and diversity of flora is impaired and intake of probiotic bacteria significantly reduced among Westerners. For example, reduction in total numbers and diversity of flora is also associated with certain chronic diseases such as inflammatory bowel disease.[87] A study from 1983 demonstrated that *Lb. plantarum,* a strong fibre fermentor, is found in only 25 % of omnivorous Americans and in about 2/3 of vegetarian Americans.[88] Great differences in volume and diversity of flora have also been observed between different human cultures. It is reported that Scandinavian children have compared to Parkistani children a much reduced flora.[89]

Astronauts, who return from space flights have during the flight lost most of their commensal flora including *lactobacillus* species such as *Lb. plantarum* (lost to almost 100%), *Lb. casei* (lost to almost 100%), *Lb. fermentum* (reduced by 43%), *Lb. acidophilus* (reduced by 27%), *Lb. salivarius* (reduced by 22%) and *Lb. brevis* (reduced by 12%),[90] changes most likely attributed to poor eating (dried food, no fresh fruits and vegetables) and a much reduced intake of plant fibers and natural antioxidants, to the mental and physical stress and eventually also to the lack of physical exercise. Many individuals in Western Societies exhibit a type of "astronaut-like lifestyle" with unsatisfactory consumption of fresh fruits, vegetables, too much stress and no or little outdoor/sport activities. Furthermore, flora seems not to tolerate exposure to chemicals including pharmaceuticals. This is also demonstrated in critically ill, who most often have lost their entire *lactobacillus* flora.[91] A recent Scandinavian study suggest that fiber-fermenting lactobacilli such as *Lb. plantarum, Lb. rhamnosus* and *Lb. paracasei* ssp *paracasei,* present in all humans with a rural lifestyle, are only found 52%, 26% and 17% respectively of persons with a more urban Western type lifestyle.[92] These lactobacilli are present in all with more rural lifestyle. The lack of these lactobacilli is probably negative as these lactobacilli are unique in their ability to ferment important fibers such as inulin and phlein, otherwise resistant to fermentation by most *lactobacillus* species,[93] and superior to other *lactobacillus* in their ability to eliminate pathogenic microorganisms such as *Clostridium difficile*.[94] Thus, the lower presence of intestinal bacteria may influence the production of bioactive antioxidants from vegetables.

Conclusive remarks

To use medicinal plants and their active components is becoming an increasingly attractive approach for the treatment of various inflammatory disorders among patients unresponsive or unwilling to take standard medicines. Food derivates have the advantage of being relatively non-toxic. Within them, curcuminoids, such as curcumin, are chemopreventive agents from turmeric curry foods. Its bioavailability on oral supplementation is low but also its toxicity. Several studies has demonstrated a number of beneficial properties on inflammatory chronic diseases such as atherosclerosis, cancer, diabetes, gastric, hepatic, pancreatic, intestinal neurodegenerative, ocular and respiratory diseases as well as on tobacco smoke-induced injuries.

Mechanisms of action are related to its antioxidant activity, able to neutralise oxygen and nitrogen reactive species, antiinflamatory properties, by decreasing activation of NF-κB and inhibiting COS-2, iNOS, LOX, LT, cytochrome P450 isoenzymes, TGF-β and fibrogenesis, and also to its immunosuppressive capacity, able to modulate cytokine and chemokine production. On the other hand, curcumin is able to prevent carcinogen activation.

References

1. World Health Organisation. Process for a global strategy on diet, physical activity and health. WHO Geneva February 2003.
2. Gil A, Bengmark S. Advanced glycation and lipoperoxidation end products amplifiers of inflammation: the role of food. *Nutr Hosp* 2007; 22: 625-640.
3. Bengmark S. Acute and "chronic" phase response – a mother of disease. *Clin Nutr* 2004; 23: 1256-1266.
4. Bengmark S. Bio-ecological Control of the Gastrointestinal Tract: The Role of Flora and Supplemented Pro- and Synbiotics. *Gastroenterol Clin North Am* 2005; 34: 413-436.
5. Bengmark S. Impact of nutrition on ageing and disease. *Curr Opin Nutr Metab Care* 2006; 9: 2-7.
6. Sharma RA, Ireson CR, Verschoyle RD et al. Effects of dietary curcumin on glutathione S-transferase and malonaldehyde-DNA adducts in rat liver and colonic mucosa: relationship with drug levels. *Clin Cancer Res* 2001; 7: 1452-1458.
7. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med* 1998; 64: 1167-1172.
8. Shapiro TA, Fahey JW, Wade KL, Stephenson KK, Talalay P. Human metabolism and excretion of cancer chemoprotective glucosinolates and isothiocyanates of cruciferous vegetables. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 1091-1100.
9. Bravani Shankar TN, Shantha NV, Ramesh HP, Murthy IA, Murthy VS. Toxicity studies on Turmeric (*Curcuma longa*): acute toxicity studies in rats, guinea pigs & monkeys. *Indina J Exp Biol* 1980; 18: 73-75.
10. Chainani.Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma Longa). *J Alternative and Complementary Medicine* 2003; 9: 161-168.
11. Grant KL, Schneider CD. Turmeric. *Am J Health-Syst Pharm* 2000; 57: 1121-1122.
12. Bernes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; 336: 1066-1071.
13. Amit S, Ben-Neriah Y. NF-kappaB activation in cancer: a challenge for ubiquitination- and proteasome-based therapeutic approach. *Semin Cancer Biol* 2003; 13: 15-28.
14. Pahl HL. Activators vand target genes of Rel/ NF-κB transcription factors. *Oncogene* 1999; 18: 6853-6866.
15. Stolina M, Sharma S, Lin Y et al. Specific inhibition of cyclooxygenase-2 restores antitumor reactivity by altering the

balance of IL-10 and IL-12 synthesis. *J Immunol* 2000; 164: 361-370.
16. Surh YJ, Chun KS, Cha HH, et al. Molecular mechanisms underlying chemo-preventive activities of anti-inflammatory phytochemicals: downregulation of COX-2 and iNOS through suppression of NF-κB activation. *Mutation Research* 2001; 480-481: 243-268.
17. Dunsmore KE, Chen PG, Wong HR. Curcumin, a medicinal herbal compound capable of inducing the heat shock response. *Crit Care Med* 2001; 29: 2199-2204.
18. Chang D-M. Curcumin: a heat shock response inducer and potential cytoprotector. *Crit Care Med* 2001; 29: 2231-2232.
19. Wallace JM. Nutritional and botanical modulation of the inflammatory cascade – eicosanoids, cyclooxygenases and lipooxygenases – as an adjunct in cancer therapy. *Integrative Cancer Therapies* 2002; 1: 7-37.
20. Began G, Sudharshan E, Udaya Sankar K, Appu Rao AG. Interaction of curcumin with phosphatidylcholine: a spectrofluorometric study. *J Agric Food Chem* 1999; 47: 4992-4997.
21. Thapliyal R, Maru GB. Inhibition of cytochrome P450 isoenzymes by curcumin in vitro and in vivo. *Food and Chemical Toxicology* 2001; 39: 541-547.
22. Jovanovic SV, Boone CW, Steenken S, Trinoga M, Kaskey RB. How curcumin preferentially works with water soluble antioxidants. *J Am Chem Soc* 2001; 123: 3064-3068.
23. Gaedeke J, Noble NA, Border WA. Curcumin blocks multiple sites of the TGF-β signaling cascade in renal cells. *Kidney International* 2004; 66: 112-120.
24. Srinisan P, Libbus B. Mining MEDLINE for implicit links between dietary substances and diseases. *Bioinformatics* 2004; 20: 1290-1296.
25. Kang BY, Song YJ, Kim KM Choe YK, Hwang SY, Kim TS. Curcumin inhibits Th1 cytokine profile in $CD4^+$ T cells by suppressing interleukin-12 production in macrophages. *Br J Pharmacol* 1999; 128: 380-384.
26. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000; 355: 134-138.
27. Groten JP, Butler W, Feron VJ, Kozianowski G, Renwick AG, Walker R. An analysis of the possibility for health implications of joint actions and interactions between food additives. *Reg Toxicol Pharmacol* 2000; 31: 77-91.
28. Kamal-Eldin A, Frank J, Razdan A, Tengblad S, Basu S, Vessby B. Effects of dietary phenolic compounds on tocopherol, cholesterol and fatty acids in rats. *Lipids* 2000; 35: 427-435.
29. Akhilender Naidu K, Thippeswamy NB. Inhibition of human low density lipoprotein oxidation by active principles from spices. *Mol Cell Biochem* 2002; 229: 19-23.
30. Kempaiah RK, Srinivasan K. Integrity of erythrocytes of hypercholesterolemic rats during spices treatment. *Mol Cell Biochem* 2002; 236: 155-161.
31. Quiles JL, Mesa MD, Ramírez-Tortosa CL et al. *Curcuma longa* extract supplementation reduces oxidative stress and attenuates aortic fatty streak development in rabbits. *Arterioscler Throm Vasc Biol* 2002; 22: 1225-1231.
32. Levi MS, Borne RF, Williamson JS. A review of cancer chemopreventive agents. *Current Medicinal Chemistry* 2001; 8: 1349-1362.
33. Anderson SR, McDonald SS, Greenwald P. *J Postgrad Med* 2003; 49: 222-228.
34. Choudhuri T, Pal S, Pal S, Agwarwal ML, Das T, Sa G. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. *FEBS Letters* 2002; 512: 334-340.
35. Shao Z-M, Shen Z-Z, Liu C-H, Sartippour MR, Go VL, Heber D, Nguyen M. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer* 2002; 98: 234-240.
36. Radhakrishna Pillai G, Srivastava AS, Hassanein TI, Chauhan DP, Carrier E. Induction of apoptosis in human lung cancer cells by curcumin. *Cancer Letters* 2004; 208: 163-170.
37. Zheng M, Ekmekcioglu S, Walch ET, Tang CH, Grimm EA. Inhibition of nuclear factor–κB and nitric oxide by curcumin induces G_2/M cell cycle arrest and apoptosis in human melanoma cells. *Melanoma Res* 2004; 14:165-171.
38. Han S-S, Keum Y-S, Seo H-J, Surh Y-J. Curcumin suppresses activation of NF-κB and AP-1 induced by phorbol ester in cultured human promyelocytic leukaemia cells. *J Biochem Molecul Biol* 2002; 35: 337-242.
39. Bharti AC, Shishodia S, Reuben JM et al. Nuclear factor-κB and STAT3 are constitutively active in $CD138^+$ cells derived from myeloma patients and suppression of these transcription factors leads to apoptosis. *Blood* 2004; 103: 3175-3184.
40. Liontas A, Yeger H. Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. *Anticancer Res* 2004; 24: 987-998.
41. Elattar TMA, Virji AS. The inhibitory effect of curcumin. Genistein, quercetin and cisplatin on the growth of oral cancer cells in vitro. *Anticancer Res* 2000; 20: 1733-1738.
42. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. *Oncogene* 2001; 20: 7597-7609.
43. Nakamura K, Yasunaga Y, Segawa T et al. Curcumin downregulates AR gene expression in prostate cancer cell lines. *Int J Oncol* 2002; 21: 825-830.
44. Hour TC, Chen J, Huang CY, Guan JY, Lu SH, Pu YS. Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing $p21^{WAFI/CIPI}$ and C/EBPβ expressions and suppressing NF-κB activation. *The Prostate* 2002; 51:211-218.
45. Deab D, Jiang H, Gao X et al. Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-κB through suppression of IκBα phosphorylation. *Mol Cancer Ther* 2004; 3: 803-812.
46. Ohadshi Y, Tsuchia Y, Koizumi K et al. Prevention of intrahepatic metastasis by curcumin in an orthotopic implantation model. *Oncology* 2003; 65: 250-258.
47. Cheng AL, Hsu CH, Lin JK et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or premalignant lesions. *Anticancer Res* 2001; 21: 2895-2900.
48. Giltay EJ, Hoogeveen EK, Elbers JMH, Gooren LJ, Asscheman H, Stehouwer CD. Insulin resistance is associated with elevated plasma total homocysteine levels in healthy, non-obese subjects. Letter to the Editor. *Atherosclerosis* 1998; 139: 197-198.
49. Mahady GB, Pendland SL, Yun G, Lu ZZ. Turmeric (*Curcuma longa*) and curcumin inhibit the growth of *Helicobacter pylori*, a group 1 carcinogen. *Anticancer Research* 2002; 22: 4179-4182.
50. Foryst-Ludwig A, Neumann M, Schneider-Brachert W, Naumann M. Curcumin blocks NF-κB and the mitogenic response in *Helicobacter pylori*-infected epithelial cells. *Biochem Biophys Res Com* 2004; 316: 1065-1072.
51. Kim M-K, Choi G-J, Lee H-S. Fungal property of *Curcuma longa* rhizome-derived curcumin against phytopathogenic fungi in greenhouse. *J Agr Food Chem* 2003; 51: 1578-1581.
52. Asai A, Miyazawa T. Dietary curcuminoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. *J Nutr* 2001; 131: 2932-2935.
53. Rukkumani R, Balasubashini S, Vishwanathan P, Menon VP. Comparative effects of curcumin and photo-irradiated curcumin on alcohol- and polyunsaturated fatty acid-induced hyperlipidemia. *Pharmacol Res* 2002; 46: 257-264.
54. Nanji AA, Jokelainen K, Tipoe GL, Rahemtulla A, Thomas P, Dannenberg AJ. Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-κB-dependent genes. *Am J Physiol Gastrointest Liver Physiol* 2003; 284: G321-G327.
55. Park E-J, Jeon CH, Ko G, Kim J, Sohn DH. Protective effect of curcumin in rat liver injury induced by carbon tetrachloride. *J Pharm Pharmacol* 2000; 52: 437-440.
56. Masubuchi Y, Enoki K, Horie T. Down-Regulation of Hepatic Cytochrome P450 Enzymes in Rats with Trinitrobenzene Sulfonic Acid-Induced Colitis. *Drug Metab Dispos* 2007; In Press.
57. Gukocvsky I, Reyes CN, Vaquero EC, Gukovskaya AS, Pandol SJ. Curcumin ameliorates etanol and nonethanol experimental pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2003; 284: G85-G95.

58. Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni JR, Das PK. Curcumin, the major component of food flavour turmeric reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. *Br J Pharmacol*. 2003; 139: 209-218.
59. Camacho-Barquero L, Villegas I, Sánchez-Calvo JM et al. Curcumin, a *Curcuma longa* constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis. *Int Immunopharmacol* 2007; 7: 333-342.
60. Jian YT, Wang JD, Mai GF, Zhang YL, Lai ZS. Modulation of intestinal mucosal inflammatory factors by curcumin in rats with colitis. *Di Yi Jun Yi Da Xue Xue Bao* 2004; 24: 1353-1358.
61. Van't Land B, Blijlevens NMA, Marteijn J et al. Role of curcumin and the inhibition of NF-κB in the onset of chemotherapy-induced mucosal barrier injury. *Leukemia* 2004; 18: 276-284.
62. Billerey-Larmonier C, Uno JK, Larmonier N et al. Protective effects of dietary curcumin in mouse model of chemically induced colitis are strain dependent. *Inflamm Bowel Dis* 2008; In press.
63. Lim GP, Yang F, Chu T et al. Ibufprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J Neurosci* 2000; 20: 5709-5714.
64. Björkman D. Nonsteroidal anti-inflammatory drug-associated toxicity of liver, lower gastrointestinal tract, and esophagus. *Am J Med* 1998; 105: S17-S21.
65. Sano M, Ernesto C, Thomas RG et al. A controlled trial of of selegiline, alpha-tocopherol, or both as treatment for Alzheimer disease. The Alzheimer disease cooperative study. *N Engl J Med* 1997; 336: 1216-1222.
66. Zhao BL, Li XJ, He RG, Cheng SJ, Xin WJ. Scavenger effects of green tea and natural antioxidants on active oxygen radicals. *Cell Biophys* 1989; 14: 175-185.
67. Sreejavan N, Rao MNA. Nitric oxide scavenging by curcuminoids. *J Pharm Pharmacol* 1997; 49: 105-107.
68. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci* 2001; 21: 8370-8377.
69. Frautschy SA, Hu W, Kim P et al. Phenolic anti-inflammatory antioxidant reversal of Aβ-induced cognitive deficits and neuropathology. *Neurobiol Aging* 2001; 22: 993-1005.
70. Ganguli M, Chandra V, Kamboh MI et al. Apolipoprotein E polymorphism and Alzheimer disease: the Indo-US cross-national dementia study. *Arch Neurol* 2000; 57: 824-830.
71. Muthane U, Yasha TC, Shankar SK. Low numbers and no loss of melanized nigral neurons with increasing age in normal human brains from India. *Ann Neurol* 1998; 43: 283-287.
72. Joseph JA, Shukitt-Hale B, Denisova NA et al. Reversal of age-related declines in neuronal signal transduction, cognitive and motor behavioural deficits with blueberry, spinach and strawberry dietary supplementation. *J Neurosci* 1999; 19: 8114-78121.
73. Rajakrishnan V, Viswanathan P, Rajasekharan N, Menon VP. Neuroprotective role of curcumin from *Curcuma longa* on ethanol-induced brain damage. *Phytother Res* 1999; 13: 571-574.
74. Thylefors B. Prevention of blindness – WHO's mission for vision. World Health Forum 1998; 19: 53-59.
75. Ughade SN, Zodpey SP, Khanolkar VA. Risk factors for cataract: a case control study. *Indian J Ophtalmol* 1998; 46: 221-227.
76. Brian G, Taylor H. Cataract blindness – challenges for the 21st century. *Bull World Health Organ* 2001; 79: 249-256.
77. Pandya U, Saini MK, Jin GF, Jin GF, Awasthi S, Godley BF, Awasthi YC. Dietary curcumin prevents ocular toxicity of naphthalene in rats. *Toxicology letters* 2000; 115: 195-204.
78. Suryanarayana P, Krishnaswamy K, Redde B. Effects on galactose-induced cataractogenesis in rats. *Molecular Vision* 2003; 9: 223-230.
79. Padmaja S, Raju TN. Antioxidant effects in selenium induced cataract of Wistar rats. *Ind J Exp Biol* 2004; 42: 601-603.
80. Punithavatihi DP, Venkatesan N, Babu M. Protective effects of curcumin against amimodarone-induced pulmonary fibrosis in rats. *Br J Pharmacol* 2003; 139: 1342-1350.
81. Illek B, Lizarzaburu ME, Lee V, Nantz MH, Kurth MJ, Fischer H. Structural determinants for activation and block of CFTR-mediated chloride currents by apigenin. *Am J Physiol Cell Physiol* 2000; 279: C1838-C1844.
82. Egan ME, Pearson M, Weiner SA et al. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. *Science* 2004; 304: 600-602.
83. Dragomir A, Björstad J, Hjelte L, Roomans GM. Curcumin does not stimulate cAMP-mediated chloride transport in cystic fibrosis airway epithelial cells. *Biochem Biophys Res Commun* 2004; 322: 447-451.
84. Ram A, Das M, Ghosh B. Curcumin attenuates allergen-induced hyperresponsiveness in sensitized guinea pigs. *Biol Pharm Bull* 2003; 26: 1021-1024.
85. Shishodia S, Potdar P, Gairola CG, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-κB activation through inhibition of IκBα kinase in human lung cancer epithelial cells: correlation with suppression of COX-2, MM-9, cyclin D1. *Carcinogenesis* 2003; 7: 1269-1279.
86. Bengmark S. Acute and "chronic" phase response – a mother of disease. *Clin Nutr* 2004; 23: 1256-1266.
87. Ott SJ, Wenderoth DF, Hampe J et al. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut* 2004; 53: 685-693.
88. Finegold SM, Sutter VL, Mathisen GE. Normal indigenous intestinal flora. In: ed. D.J. Hentges, Human intestinal microflora in health and disease. *London:Academic Press* 1983; 3-31.
89. Adlerberth I, Carlsson B, deMan P et al. Intestinal colonization with *Enterobacteriaceae* in Pakistani and Swedish hospital-delivered infants. *Acta Pediatr Scandinav* 1991; 80: 602-610.
90. Lencner AA, Lencner CP, Mikelsaar ME et al. The quantitative composition of the intestinal lactoflora before and after space flights of different lengths. *Nahrung* 1984; 28: 607-613.
91. Knight DJW, Ala'Aldeen D, Bengmark S and Girling KJ. The effect of synbiotics on gastrointestinal flora in the critically ill. Abstract. *Br J Anaesth*. 2004; 92: 307P-308P.
92. Ahrné S, Nobaek S, Jeppsson B, Adlerberth I, Wold AE, Molin G. The normal lactobacillus flora in healthy human rectal and oral mucosa. *J Appl Microbiol* 1998; 85: 88-94.
93. Müller M, Lier D. Fermentation of fructans by epiphytic lactic acid bacteria. *J Appl Bact* 1994; 76: 406-411.
94. Naaber P Smidt I, Stsepetova J, Brilene T, Annuk H, Mikelsaar M. Inhibition of *Clostridium difficile* strains by intestinal *Lactobacillus* species. *Med Microbiol* 2004; 53: 551-554.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):282-287
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Intragastric balloon and multidisciplinary team

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Abstract

***Background*: The intragastric balloon is widely used for weight reduction in obese patients, but results are variable. We describe our results enhancing the importance of a Multidisciplinary Team (MT) taking part in the treatment.**

***Methods:* A retrospective review was done concerning a total of 119 balloons , placed in 116 patients, under endoscopic control and conscious sedation, from May 2001 until August 2006. 49 patients were prepared and recommended to be followed by a MT in a physical unit, at least every 15 days during 6 months. 67 were indicated and followed by other colleagues, without MT. Removal was performed 6 months later.**

***Results:* Concerning our 49 patients, mean age was 38, 1 years, 31 female and 18 males, with BMI ranged between 32 and 63, average of 42. The average decrease of weight excess was 31, 85% (-4, 45-80, 4%), and the BMI diminished 5,3 points (from 13,6 to gain of 0,9). The treatment failed in 34,6 % of our patients —including 4 patients lost of follow-up (8, 16%)—, compared with 53, 8% of patients without structured MT for selection and follow-up. Physical exercise enhanced markedly the results with 45, 8% of excess of weight loss in women and 39, 7% in males, compared with 14, 6 and 15, 6% in patients who didn't follow the program. The weight loss was mostly fat mass, 89,9% in men and 75,6% in women.- The results maintenance was obtained in 40% of patients one year later. There were no major complications; one balloon had to be removed at 3 weeks because of intolerance, another at 5 months because of gastroesophageal reflux.**

***Conclusions:* BIB is an effective help to achieve a short term weight loss in obese patients; nevertheless, good and long lasting results will depend on the modification of life style obtained by a multidisciplinary approach.**

(*Nutr Hosp*. 2009;24:282-287)

Key words: *Intragastric balloon. Obese patients. Multidisciplinary.*

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Recibido: 29-V-2008.
Aceptado: 12-XII-2008.

BALÓN INTRAGÁSTRICO Y EQUIPO MULTIDISCIPLINAR

Resumen

***Antecedentes:* el balón intragástrico se usa ampliamente para la reducción de peso de pacientes obesos pero sus resultados son variables. Describimos nuestros resultados resaltando la importancia de la implicación del equipo multidisciplinar (EM) en el tratamiento.**

***Métodos:* Se realiza una revisión retrospectiva correspondiente a 119 balones colocados a 116 pacientes bajo control endoscópico y sedación consciente desde mayo de 2001 a agosto de 2006. Se preparó a 49 pacientes a los que se recomendó seguimiento por un EM en una unidad física, al menos cada 15 días durante 6 meses. Se indicó a 67, que fueron seguidos por otros colegas, sin un EM. Se realizó la retirada 6 meses después.**

***Resultados:* Con respecto a nuestros 49 pacientes, la edad media fue de 38,1 años, hubo 31 mujeres y 18 hombres, con un IMC en el rango de 32-63, media de 42. El descenso medio de exceso de peso fue de 31,85% (-4,45-80,4%), y el IMC disminuyó en 5,3 puntos (desde 13,6 a una ganancia de 0,9). El tratamiento fracasó en el 34,6% de nuestros pacientes —incluyendo 4 pacientes (8,16%) en quienes se perdió el seguimiento— en comparación con el 53,8% de pacientes sin un EM estructurado para la selección y el seguimiento. El ejercicio físico aumentó significativamente los resultados con un 45,8% de exceso de pérdida de peso en las mujeres y un 39,7% en los hombres, en comparación con el 14,6 y 15,6% en los pacientes que no siguieron el programa. La pérdida de peso fue sobre todo de masa grasa, 89,9% en los hombres y 75,6% en las mujeres. Los resultados se mantuvieron en el 40% de los pacientes un año después. No hubo complicaciones importantes; se tuvo que retirar un balón a las 3 semanas por intolerancia, y otro a los 5 meses por reflujo gastroesofágico.**

***Conclusiones:* El BIG es una ayuda eficaz para conseguir una pérdida de peso en el corto plazo en pacientes obesos; sin embargo, los resultados buenos y duraderos dependerán de la modificación del estilo de vida obtenida mediante un abordaje multidisciplinar.**

(*Nutr Hosp*. 2009;24:282-287)

Palabras clave: *Balón intragástrico. Pacientes obesos. Multidisciplinar.*

Introduction

The Bioenterics Intragastric Balloon (BIB) was introduced almost a decade ago, and tested in a preliminary study of patients by Dr. Mathus-Vliegen,[1] demonstrating its innocuousness and efficiency helping to achieve an around 10-15% weight loss. Later, several published series obtained in general good results, especially at a short delay.[2-9]

Certainly a lot of questions subside, especially concerning patients' selection, results at long term, and the influence of specialized teams in the achievement of good results.

Since 1991, the INH enunciated the procedure to indicate the suitable surgical treatment for the obese patient.[10] It includes the need of a Multidisciplinary Team (MT). Nevertheless, the Intragastric Balloon (BIB), a more recent invasive therapeutic modality, suffers still poorly definite protocols, the influence of MT not being known yet in the results and its maintenance.

We analyze our results with regard to the application of the BIB in EM'S context.

Patients and methods

Patients

From May 2001 until August 2006, a total of 119 balloons were placed in 116 patients. Of these, 49 were treated entirely by our team. We placed the other 67 as well but they were indicated and followed by other colleagues, in MT'S absence. We proceed to review retrospectively the data of all these patients, and evaluate results of the technique in both groups in term of weight loss, and the eventual benefit of a MT following in our own patients.

We indicate the BIB to patients with an obesity of more than 2 years of evolution in which the non invasive methods have failed, if they promise to submit to the discipline of our MT, and if they are considered to be suitable by our psychologist.

There are contraindications like mental problems, drug or alcohol addiction, non stable cardiovascular disease, or the presence of previous gastric surgery. An active ulcerous gastro-duodenal disease is a temporal contraindication as well as known or detected disorders of food behavior, except advice of psychologist foreign to the team (table I).

The lack of availability to the follow-up or the denial of the patient to accept the practice of the physical exercise as part of the treatment was also at least temporary contraindications.

Table I
Contraindications to the gastric balloon treatment

a) Psyquiatric disorders
b) Drug addiction, alcoholism.
c) Active gastro duodenal disease.
d) Inflammatory bowel disease, malignancies.
e) Hematologic disorders.
f) Pharmacologic treatments like anticoagulants, antiinflamatories, corticoids, AAS.
g) Hearth or renal diseases able to be decompensate by first days vomiting. In general, medical contraiindicacions to bariatric surgery.
h) Lack of guaranties to be able to retire de balloon in the next 48 hours in case of deflation.
i) Extreme ages, being accepted in general 18 and 65 years.

Multidisciplinary Team and Follow-up

Our team, whose composition is considered essential in the treatment of the obese patient, consists of a medical coordinating surgeon, endoscopist, a psychologist specialized in cognitive-behavioral skills, a dietitian and a physical trainer specialized in the obese patient treatment.

The follow-up consists of reviews at least fortnightly, of sequential form for all the members of MT in a physical unit.

Contrary to other tendencies,[2,4,5,8,9] our dietitian does not impose predefined diets of 800 or 1,000 calories. Departing from the culinary preferences and habits of the patient, the dietician proceeds to their progressive modification.

The psychologist provides a preliminary study of personality, test of anxiety, detection of disorders of food behavior, and cognitive-behavioral support to the proposed changes of life; the patient continued to be evaluated and followed every 15 days during 6 months and more recently, every 3 months for 2 years, allowing application of psychotherapy if needed in some cases, relaxation techniques in case of stress or anxiety, and, in any case, promoting the application of life habits changes.

The physical trainer evaluates the patient at the beginning and at 6 months: a complete anthropometry is done with measure of 6 perimeters and 6 folds, as well as dynamometry and anaerobic limit. The patient was individually trained during 6 months, twice weekly and recommendation was done to train at least 40 minutes 6 days per week.

The surgeon is the medical coordinator and takes care of the clinical aspects of the obese patient, studies carefully the metabolic syndrome and eventual vitamin and mineral deficiencies, to optimize patient's general health. Body composition was determinate by impedantiometry, and repeated at each patient's visit.

Every patient was evaluated by the whole team, and the strategy carefully discussed with the patient who was prepared and meanwhile informed of all the possibilities of improvement of his obesity, including surgical techniques.

Table II
49 patients followed with intragastric balloon

Sex	*Females*	*Males*
Number	31	18
Mean age	37.7 (20-63)	39.5 (24-60)
Initial BMI	41.88 (31.8 -63)	41.63 (33-62.3)
BMI loss	5.77 (-1.1-13.6)	4.43 (-0.6-9.4)
% Ew loss	35.2 (0-120)	23.4 (0-50)
% Ew loss with physical exercise	39.7% (22 patients)	45.8% (11 patients)

Once the balloon was the elected technique, it was introduced by the endoscopist, assisted by the medical coordinator.

Balloon Placement and Removal

BioEnterics's BIB is a globe of silicone with capacity from 400 to 700 cc according to the manufacturer, whose filling is usually done with 500 cc, to achieve a partial occupation of the stomach, creating a sensation of precocious satiety, and decrease of the appetite. Indeed, its mechanism of action is not well known, but it seems to work mainly through expansion of the antral gastric wall,[11] as well as of a marked slowing down of the gastric digestion.[12]

To the filling, we add to the saline serum 10 cc of blue of methylene, in order to detect an eventual escape through the valve, before its retreat foreseen before 6 months of its application. All the balloons were filled by 500 cc, except in patients to whom the second or third balloon was applied, or in a patient's case with precedents of bulimia, in which, the globe was filled by 550 cc.

The introduction of the BIB is done by endoscopy, and under sedation, as well as its retreat, routinely planned for 6 months. In two patients general anesthesia was used because of phobia to the introduction of objects oral route.

We tried to avoid the complications described up to the date:

1.º BIB's migration and bowel occlusion[3,5] by means of retreat before 6 months and addition of 10 cc of blue of methylene to the saline serum. In case of precocious deflation, the BIB would be withdrawn before 48 h.

2.º Nauseas and vomits tried to be weakened by means of systematic administration of ondasetron during the procedure and 8 mg every 12 hours during the first 3 days. Liquid diet was delayed up to 24-36 h.

In spite of it, the tolerance was very changeable and we encourage the patients to overcome these days trusting that these symptoms correspond to the stomach adjustment to the BIB and they will yield spontaneously.

3.º The initial aggravation of a previous gastroesophagic reflux (RGE) was well controlled increasing Omeprazol to 40 mg daily.

4.º The episodes of possible food retention and/or transitory gastroparesis were managed with dietetic modification.

Data Analysis

We choose to express our result attending to the percentage of lost overweight, taking as ideal weight the correspondent to the Body Mass Index(BMI), preferring the reference of 25[6] to the more demanding 22.[13] The immediate success was defined as a loss of weight excess superior to 20%.[8] We analyze likewise the variation of corporal composition, attending principally to the proportion of fat lost with regard to the global weight decrease, and therefore fat free mass conservation.[14]

Results

With regard to the 49 own patients, there were 31 women with a mean age of 37,7 years and 18 males with average of 39,5 years. The BMI ranged between 31,8 and 63 for women and 33 and 62,3 for the men with average of 41,88 and 41,63 respectively.

There were no such technical complications as viscous injuries or precocious deflation. There was a case of globe extraction before 3 months because of intolerance in a patient under antidepressant treatment. We observe a case of reflux esophagitis aggravated by the BIB, as well as gastritis with erosive diffuse injuries[2] in a patient with episodes of gastric retention, and therefore, globe withdrawal at 5 months.

In 5 patients, it was necessary to postpone the retreat because gastric solid remains were observed at endoscopy. Two male patient and three young women insisted on the sensation of ineffectiveness of the balloon.

The nauseas, vomits and transitory constipation in most patients were considered to be collateral effects of the treatment, and were controlled partially by pharmacological treatment. They were not assessed therefore as complications.[6]

Other minor problems like constipation and halitosis were easily treated by conventional methods.

We do not observe any case of candidiasis on the BIB at its retreat.

There was a case of late abdominal pain due to biliary stones, which was controlled and treated surgically after balloon was retired.

The tolerance to the physical exercise was excellent, without injuries, and with marked positive effect on state of mind and motivation, as well as with a degree of adherence of the 67, 34%, which was especially high in the 2ª half of our experience reaching 80%.

The average decrease of the weight excess was 31, 85% with a great variability, from gain of 4, 45% up to

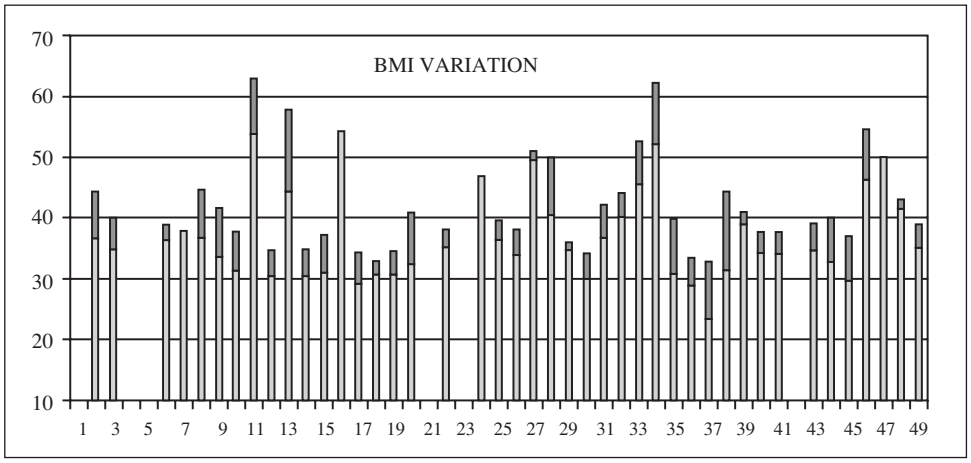

Fig. 1.—Each column indicates decrease of a patient BMI after balloon retraction, colored in red.

loss of 80% excess of weight. In the consulted studies,[2-9] the average decrease of the weight excess ranged from 10 to 48.3%.

In terms of BMI, after de balloon was removed, it decreased 5, 3 points, varying from a loss of 13, 6 to a gain of 0, 9. The final average BMI was 36, 4 between 23, 4 and 54, 6 (fig. 1).

The loyalty of the patients to the program of physical exercise produced a marked implementation of the results: in the women, the percentage of weight excess loss was 45, 8% in contrast with those who did not expire with the program, which lost only 14, 6% of their weight excess. In the males, there was 39, 7% of loss of weight excess with exercise, opposite to 15,6 % without it (fig. 2).

Seventeen —34.6%— of our patients lost less than 20 % of their weight excess, which means failure of the treatment (we include here the patients lost of follow-up).

Comparing roughly our casuistry with 62 patients deprived of multidisciplinary follow-up, the index of failure in these reached 53, 8%.

The successive utilization of 2.º balloon in 3 patients did not really improve the results.

We suffered a total loss of follow-up of 8, 16% (4 patients) in our group compared to the published results of 7.4-33.1%.[2-9] The patients came to remove their balloon, but refused to be weighted (we assumed then no weight loss).

The results were kept at least during a year in 40% of the patients.

We obtained favorable results in relation to the impedanciometry: a preponderant decrease of fat was observed with regard to the total lost weight, being 89, 8% in males and 75, 6% in women (fig. 3). This aspect has not been described in the literature with regard to the BIB, although it has been done in bariatric surgery by authors like Metcalf.[14] In this respect,

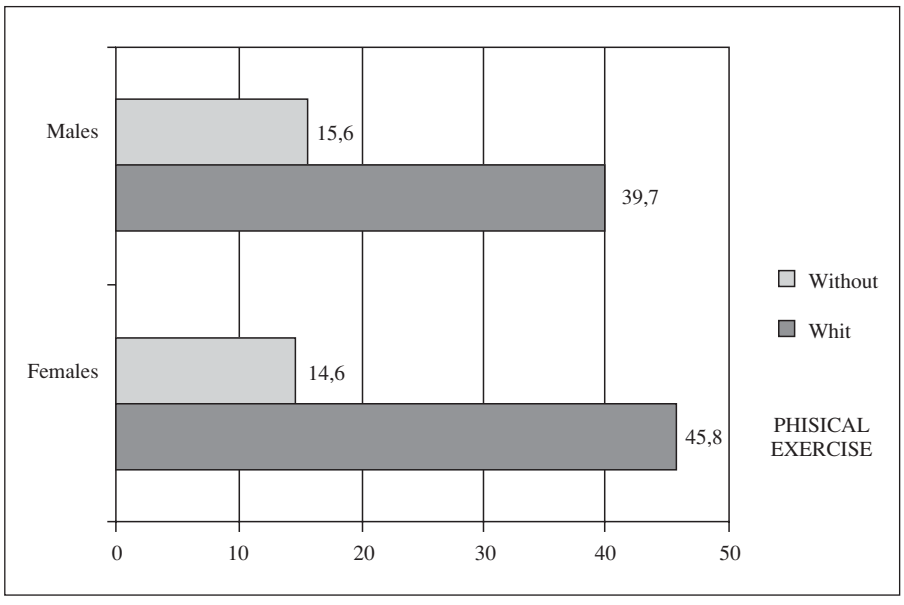

Fig. 2.—Percentage of excess of weight loss.

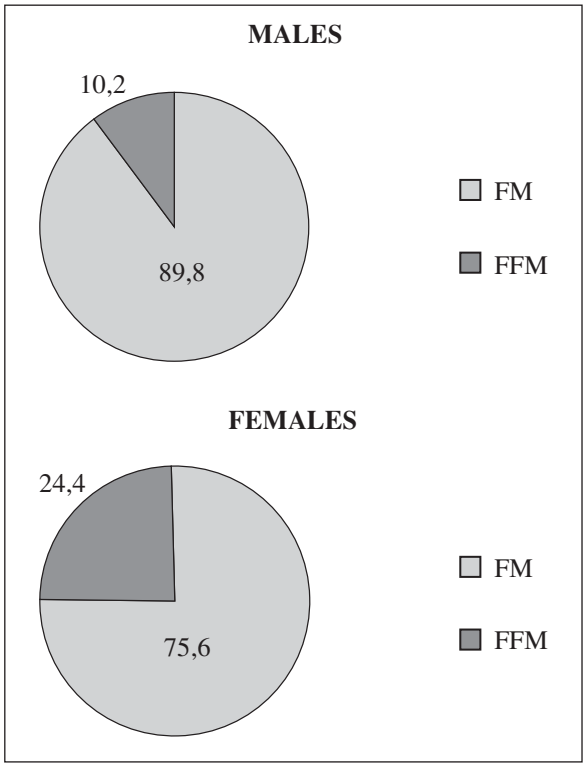

Fig. 3.—Percentage of fat mass (FM) and fat free mass (FM) loss.

we consider key the participation of personal trainers in MT.

Discussion

The BIB has demonstrated to be an effective and slightly invasive method in the treatment of the obesity. Its principal disadvantage takes root in the eventual sharp and short lasting weight loss. This may create problems like frustration and aggravation of patient's psychosocial problems, as well as others like colelithiasis, nephritic colic, or dehydration with risk of cardiovascular complications, besides the metabolic consequences still badly known concerning these changes.

We understand that this technology has to be applied only in case of previous failure of not invasive methods to lose weight, and exclusively in the context of a Multidisciplinary Team capable of modifying, if possible in the space of 6 months, the patient's habits of life.

Because of this, the Team must be expert and the patient disciplined.

In the checked works, stands out the scanty precision relating to the follow-up of the patients treated by means of BIB.[2,3,5,6,7,9] The multicentre Brazilian series is the only one that precise the intervention of a personal trainer in the MT[8].

In two of these series, the weight loss average was less than 20% of the overweight, which suggests failure of the technique.[3,4] It would be important to analyze the reasons of variability of results of the same technique used by different groups.

Our own experience shows an implementation of the results if the technique combined with the monitored physical exercise: in this case, the loss of overweight obtained was more than double than in the most sedentary patients.

Of equal way, the lack of a multidisciplinary team in the treatment of the patient, enhance the percentage of failures to the unacceptable number of 53, 8%.

We rise this way a double problem: the selection of the patient, with absence of current suitable criteria (apart the acquaintances BMI, age and eventual contraindications); on the other hand, the training of the professionals who indicate and/or apply the BIB.

This way applied, the technique provokes very scanty complications: there were neither migrations nor perforations, nor dehydrations nor fluid imbalances clinically significant. We attribute a case of balloon intolerance with retreat at 3 months because a lack of selection.

Nevertheless, our main problem was the lack of response of some patients to the treatment: in 3 cases we believe that it was due to non diagnosed food behavior disorder; nevertheless in 2 males, there was a total lack of perception of the presence of the BIB, and the weight loss was owed exclusively to the will of the patient and to the support of MT. We understand that a great variability exists in the mechanical efficiency of the BIB depending on the degree of antral distension generated. We do not know the way of foreseeing this situation.

On the other hand, the contribution of an intensive program of physical exercise carried out by personal specializing trainers, had the double advantage of promoting a weight loss fundamentally based on fat mass, and further, we know with a C degree of evidence that it contributes decisively to the supported weight loss. A 40% of maintenance of results a year is similar to the reported one for HERVE,[15] who insists on the need of modification of habits by a MT, which begins 8 to 12 weeks before the insertion of the BIB.

Our therapeutic approach is based on the conviction that the obesity is a chronic disease, which does not have a known curative treatment, with a persistent tendency to the weight increase independently of the applied treatment. The treatment is therefore based on the alteration of habits, with major or minor therapeutic support.

We consider that MT is basic in the treatment of our patients, whereas the complementary applied treatment, being dietetic - pharmacological, an Intragastric Balloon or a gastric band, is based on the principle of the "minimal effective dose". We apply the less invasive procedure for every patient, trying to avoid side effects tied to these techniques, and to involve as much as possible the effort of the own patient in his treatment.[16]

We have to clarify that the time invested by patient and Team in this type of treatment is considerable:

approximately 73 total hours in 6 months of attention for the Team, to which there would be necessary to add up the time for the regular practice of physical exercise. We have to admit that this approach is difficult to apply nowadays in the Public Health, for what it is probable that the minimally invasive technologies are less successful in this area.

Of equal way, the terrible results described in those patients deprived of multidisciplinary follow-up suggest us that it is not correct to propose this technique without to rely on a MT. The lack of motivation to follow this methodology must be a contraindication for the procedure.

With regard to the results, we do not believe suitable to qualify a weight loss superior to 50 % in 6 months as "very good" as suggests Wahlen,[17] provided that it might represent in some cases a relative intolerance to the BIB, accompanied by retention vomits or sometimes a turn towards a disorder of food behavior type anorexia.

Let's not forget, that has been demonstrated that the loss of the fat free mass (FFM) is correlated in a linear way by the degree of weight loss, indicating that a rapid loss of weight can result in a disproportionately high loss of muscular mass.

On the contrary, if we accept that the correct weight loss should be an average of half to one kilo per week, the total should range at 6 months between 12 and 24 kilos, independently of the initial weight.

We think also that it is important to mention, not only the average percentage of lost overweight and his range, but the number of patients who achieved a good result. The consensus seems today to express as failure a weight loss lower than 20% of the weight excess. In effect, the variability of response is very wide, and the average of percentage of weight loss is obtained on the basis of an average of bad results and maybe some excesses of weight loss.

Likewise, it is important to achieve a weight loss concerning a maximum of fat mass (FM), with conservation, or ideally increase, of fat free mass (FFM).

Ideally, the results of the obesity treatments should concern the qualitative aspect of weight loss, instead of the gross weight. In a recent controlled series of 39 patients treated by gastric By-Pass, we can observe a loss of 59, 7% of the weight excess at 6 months, but also a decrease of 7, 8 kg of FFM, which is not desired. In this study, the body composition was measured up on the basis of the total body water measured by means of deuterium oxide isotopic dilution.[18] Our problem is that today the method we have used, the impedanciometry, is undoubtedly comfortable in the practice, but of scanty precision.

The weight maintenance at one year has been obtained in 40% of the patients: this information compared with non invasive methods is excellent, but he has to be improved. Our first measure has been to the follow-up, for all treated patients, up to 2 years.

In conclusion, treatment by means of BIB is useful in the context of a MT. It has to include if possible a physical trainer, provided that he seems to have a marked influence on the degree and the quality of the weight loss.

References

1. Mathus-Vliegen EM, Tygat GN. Intragastric balloons for morbid obesity: results, patient tolerance and balloon lifespan. *Br J Surg* 1990; 77: 76-9.
2. Totte E, Hendrickx L, Pauwels M, Van Hee R. Weight reduction by means of intragastric device: experience with the Bio-Enterics's intragastric balloon. *Obes Surg* 2001; 11: 519-23.
3. Evans JD, Scott MH. Intragastric balloon in the treatment of patients with morbid obesity. *Br J Surg* 2001; 88: 1245-8.
4. Hodson RM, Zacharoulis D, Goutzamani E, Slee P. Management of obesity with the new Intragastric Balloon. *Obes Surg* 2002; 11: 327-9.
5. Doldi SB, Micheletto G, Perrini MN, Librenti MC et al. Treatment of obesity with intragastric balloon in association with diet. *Obes Surg* 2002; 12: 583-7.
6. Al-Momen A, El-Mogy I. Intragastric balloon for obesity: A retrospective evaluation of tolerance and efficacy. *Obes Surg* 2005; 15: 101-5.
7. Roman S, Napoleon B, Mion F, Bory RM et al. Intragastric balloon for "non-morbid" obesity: a retrospective evaluation of tolerance and efficacy. *Obes Surg* 2004; 4: 539-44.
8. Sallet JA, Marchesini JB, Paiva DS, Komoto K et al. Brazilian multicenter study on the intragastric balloon. *Obes Surg* 2004; 14: 991-8.
9. Genco A, Bruni S, Doldi B, Forestieri P et al. Bioenterics Intragastric Balloon: the Italian experience with 2,515 patients. *Obes Surg* 2005; 15: 1161-4.
10. Gastrointestinal Surgery for Severe Obesity. NIH Consensus Statement 1991; 9 (1): 1-20.
11. Geliebter A, Hashim SA. Gastric capacity in normal, obese and bulimic women. *Physiol Behav* 2001; 74: 743-6
12. Bonazzi P, Petrelli MD, Lorenzini I, Peruzzi E et al. Gastric emptying and intragastric balloon in obese patients. *Eur Rev Med Pharmacol Sci* 2005; 9: 15-21
13. Lemmens HJ, Brodsky JB, Bernstein DP. Estimation ideal body weight. *Obes Surg* 2005; 15: 1082-3.
14. Metcalf B, Rabkin RA, Rabkin JM, Metcalf L et al. Weight loss composition: the effects of exercise following obesity surgery as measured by bioelectrical impedance analysis. *Obes Surg* 2005; 15: 183-6.
15. Herve J, Wahlen CH, Schaeken A, Dallemagne B et al. What becomes of patients one year after the intragastric balloon has been removed? *Obes Surg* 2005; 15: 864-70.
16. Mazure Lehnhoff RA, Salgado Mijail G, Valencia A, Villarreal P et al. Ejercicio físico y cirugía bariátrica. *Nutr Hosp* 2007; 22: 397-401.
17. Wahlen CH, Bastens B, Herve J, Malm Endier C et al. The Bioenterics Intragastric Balloon (BIB): how to use it. *Obes Surg* 2001; 11: 524-7.
18. Carrasco F, Papapietro K, Csendes A et al. Changes in resting energy expenditure and body composition after weight loss following Roux-en-Y gastric bypass. *Obes Surg* 2007; 17: 608-616.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):288-296
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Anti-inflammatory effect of parenteral fish oil lipid emulsion on human activated mononuclear leukocytes

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Abstract

Background & aim: **To compare the effect of fish oil-based (FO) lipid emulsions (LE) for parenteral administration with standard LE and a new FO containing LE composed of four different oils on the antigen presentation and inflammatory variables.**

Methods: **Phytohemagglutinin (PHA) activated human mononuclear leukocytes were cultured with different LE - Control: without LE; SO: soybean oil; SO/FO: soybean and FO (4:1); MCT/SO: medium chain triglycerides and SO (1:1); MCT/SO/FO: MCT/SO and FO (4:1) and SMOF: a new LE containing FO. Cytokine production was evaluated by ELISA, the expression of antigen-presenting and co-stimulatory surface molecules were analyzed by flow cytometry and lymphocyte proliferation was assessed by H^3-Thymidine incorporation, after tetanus toxoid-induced activation.**

Results: **All LE decreased the HLA-DR and increased CD28 and CD152 expression on monocytes/macrophages and lymphocytes surface ($p < 0.05$). SO/FO and MCT/SO/FO decreased lymphocyte proliferation ($p<0.05$). All LE decreased IL-2 production, but this effect was enhanced with MCT/SO/FO and SMOF ($p < 0.05$). MCT/SO/FO decreased IL-6 and increased IL-10, whereas SO had the opposite effect ($p < 0.05$).**

Conclusion: **FO LE inhibited lymphocyte proliferation and had an anti-inflammatory effect. These effects seem to be enhanced when FO is mixed with MCT/SO. SMOF had a neutral impact on lymphocyte proliferation and IL-6 and IL-10 production.**

(*Nutr Hosp*. 2009;24:288-296)

Key words: *Lipid emulsion. Soybean oil. Fish oil. Co-stimulatory molecules and antigen presentation.*

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Recibido: 3-IX-2008.
Aceptado: 2-III-2009.

EFECTO ANTIINFLAMATORIO DE LA EMULSIÓN PARENTERAL DE LÍPIDOS CON ACEITE DE PESCADO EN LEUCOCITOS MONONUCLEARES HUMANOS ACTIVADOS

Resumen

Antecedentes & objetivo: **Comparar el efecto de las emulsiones lipídicas (EL) basadas en aceite de pescado (AP) para la administración parenteral con las EL estándar y una nueva EL que contiene AP compuesta por cuatro aceites distintos sobre la presentación antigénica y las variables inflamatorias.**

Métodos: **se cultivaron leucocitos mononucleares activados con fitohemaglutinina (PHA) con diferentes EL - Control: sin EL; AS: aceite de soja; AS/AP: soja y AP (4:1); TCM/AS: triglicéridos de cadena media y AS (1:1); TCM/AS/AP: TCM/AS y AP (4:1) y SMOF: una nueva EL que contiene AP. Se evaluó la producción de citocinas mediante ELISA, se analizó la expresión de moléculas de superficie de presentación de antígeno y co-estimuladoras mediante citometría de flujo y se evaluó la proliferación linfocitaria mediante la incorporación de timidina-H^3 tras la activación inducida por el toxoide tetánico.**

Resultados: **Todas las EL disminuyeron la expresión de HLA-DR y aumentaron la expresión de CD28 y CD152 sobre superficie de monocitos/macrófagos y linfocitos ($p < 0,05$). La AS/AP y la TCM/AS/AP disminuyeron la proliferación linfocitaria ($p < 0,05$). Todas las EL disminuyeron la producción de IL-2, pero su efecto se incrementó con las emulsiones TCM/AS/AP y SMOF ($p < 0,05$). La TCM/AS/AP disminuyó la IL-6 y aumentó la IL-10, mientras que el AS tuvo el efecto opuesto ($p < 0,05$).**

Conclusión: **La EL AP inhibió la proliferación linfocitaria y tuvo un efecto antiinflamatorio. Estos efectos parecen estar potenciados cuando el AP se mezcla con TCM/AS. La SMOF tuvo un efecto neutro sobre la proliferación linfocitaria y la producción de IL-6 e IL-10.**

(*Nutr Hosp*. 2009;24:288-296)

Palabras clave: *Emulsión lipídica. Aceite de soja. Aceite de pescado. Moléculas co-estimuladoras y presentación antigénica.*

Introduction

Fatty acids can modulate the immune and inflammatory response in in vitro and in vivo studies.[1-3]

Patients with indication for parenteral nutrition receive fatty acids (FA) as lipid emulsions (LE) for parenteral administration. Depending on the fatty acids composition, LEs can have different impacts on immune functions, and thus affect the patient's clinical course.[4-7]

The immune response triggered by antigen presentation involves the active participation of different cell-surface molecules with immune functions.[8,9] The antigens that undergo phagocytosis by monocytes/macrophages and other antigen-presenting cells are expressed on the cell surface by MHC class II molecules (also known as HLA molecules) because they are recognized by T-helper lymphocytes.[8,9]

Additionally, the effective activation of the T-helper lymphocytes also depends on the signal triggered by the interaction between the co-stimulatory molecules —CD80 and CD86— found on the surface of monocytes/macrophages, and their receptor CD28.[10,11] Without the second co-stimulatory signal, the T-helper lymphocyte does not recognize the antigen as a stimulant and develops immune tolerance.[12]

After being activated, the immune cells start to produce several pro- and anti-inflammatory cytokines that mediate the immune response against pathogenic agents.

The activation level of the T-helper lymphocytes is controlled by the surface molecule CD152, an alternative ligand for CD80 and CD86 molecules. The interaction between CD152 and the co-stimulatory molecules CD80 and CD86, inhibits the cell activation cascade, preventing enhancement of the immune response.[13,14]

The new goals of parenteral nutrition therapy for the critically ill include mitigation of inflammation and modulation of the immune system via immunomodulating nutrients, such as n-3 polyunsaturated fatty acids (n-3 PUFA). The n-3 PUFA have shown reduced inflammatory effects and clinical benefits such as shorter hospital stays and a potential decrease in morbidity and mortality rates.[15-17]

Therefore, it is worth studying the in vitro effects of parenteral lipid emulsions containing fish oil, rich in n-3 PUFA, on the expression of human mononuclear leukocytes surface molecules that participate in the antigen-presentation process, cytokine production and lymphocyte proliferation.

Materials and methods

Ethical statement

All experimental procedures of the current study were previously approved by the local Ethical Scientific Committee.

Selection of volunteers and collection of mononuclear cells

Samples of peripheral blood were drawn from volunteers - healthy male donors (n = 10), 20-40 years of age, non-smokers, mild exercise activity (less than twice a week), non-drinkers of alcohol, non-users of drugs and with history of no disease condition near (3 weeks) the date blood was collected.

Mononuclear cells were obtained by the Ficoll Hypaque gradient method (Histopaque 1077, Sigma - USA). They were then resuspended in a RPMI medium (RPMI 1640, Gibco-USA), containing 2 mmol/L L-glutamine, 25 mM/L Hepes medium, 0.07 mM/L gentamicin and $1x10^5$ U/L penicillin with 10% inactivated FBS (Fetal Bovine Serum) (Gibco-USA).

Lipid Emulsions and Study Groups

The lipid emulsions available on the market and used in this study have already been described.[5]

Six groups were established based on the type of lipid emulsion added to the culture medium (table I).

Cell cultures to evaluate the expression of surface molecules, determine the lipid profile of the cell membrane and the production of cytokines

Costar 24-well cell culture plates were used to incubate $2x10^6$ mononuclear cells with viability above 95% (as accessed by Tripan Blue exclusion) under humid atmosphere, with 5% of CO_2 at 37 ºC for 24, 48 and 72 hours in 2 mL RPMI 1640 culture medium (Gibco-USA), containing 10% of inactivated FBS (Gibco-USA), 2 mmol/L L-glutamine, 25 mM/L Hepes, 0.07 mM/L gentamicin and $1x10^5$ U/L penicillin, in 10 µg/mL phytohemagglutinin (Phytohemagglutinin = PHA) (Sigma-USA). Different parenteral LEs were

Table I
Experimental groups

Experimental groups	*Lipid emulsions added to the culture media*
Control	No lipid emulsion added
SO	Lipovenoes® LCT 20%
SO/FO	Lipovenoes® LCT 20% enriched with Omegaven® 10% (4:1)
MCT/SO	Lipovenoes® MCT 20%
MCT/SO/FO	Lipovenoes® MCT 20% enriched with Omegaven® 10% (4:1)
SMOF	SMOFlipid® 20% (30% soybean oil/30% MCT/25% olive oil/ 15% fish oil

® Fresenius Kabi.

added at the concentration of 1 mg/mL to make up the six experimental groups.

Separation of mononuclear cell membranes and gas chromatography

The monocytes/macrophages and lymphocytes of each experimental group were submitted to five cycles of freezing/defreezing in liquid nitrogen. Then the pool of cells of each group was centrifuged at 5,000 rpm for five minutes at 4 ºC. The supernatant was collected and centrifuged for 60 minutes at 30,000 rpm at 4 ºC.[18]

Then, the fatty acids of the cell membrane were extracted and sterilized using the Folch method.[19] Membrane composition was determined by gas chromatography (Shimadzu CG2010AF-Japan), equipped with a splint/splintless injector, flame ionization detector (FID) and a fused silica capillary column - 100 m long, 0.25 µm internal diameter and 0.20 µm film. (Omegawax 2560, Supelco-Japan).

A 37-fatty acid standard was used (FAME Standard Supelco 37-Component FAME Mix, Supeco-Japan). One mL of the sample was analyzed in the splintless mode at 270 °C, column with initial temperature fixed at 60 ºC with temperature ramp rate of 3.5 ºC/min until it reached 240 ºC. The detector temperature was maintained at 300 ºC.

Analysis of the expression of surface molecules by flow cytometry

Forty-eight hours later, the cells that had not adhered to the culture plate were discarded and only adherent monocytes/macrophages were labeled with the following anti-human monoclonal antibodies: CD14 APC, HLA-DR Cy-Chrome, CD80 FITC and CD86 PE (BD Biosciences, USA) and their respective isotype controls: mouse IgG2a APC, mouse IgG2a,k Cy-Chrome, mouse IgG1 FITC and mouse IgG2b,k PE (BD Biosciences, USA). Seventy-two hours later, the non-adherent cells were labeled with monoclonal antibodies specific to T-helper lymphocytes - anti-human CD3 Cy-Chrome, anti-human CD4 APC, anti-humanCD28 FITC and anti-humanCD152 PE (BD Biosciences, USA) and their respective isotype controls - mouse IgG1,k cy-chrome, mouse IgG1,k APC, mouse IgG1 FITC and mouse IgG2a PE (BD Biosciences, USA). After being labeled, the cells were examined by flow cytometry (FacsCalibur Becton & Dickson-USA). Aliquots of monocytes/macrophages incubated for 48 hours and lymphocytes cultured for 72 hours were collected for determining the lipid profile of the cell membrane.

Analysis of cytokine production

To measure cytokine production, samples of the mononuclear cells cultured with the different parenteral LEs and activated with PHA were collected after 24-hours to analyze the production of IL-2 and IL-6 and after 48-hours for IL-10. The samples were stored in liquid nitrogen immediately after collection for later measurement of cytokine production by ELISA, using specific kits (Human IL-2 ELISA Set, Human IL-6 ELISA Set and Human IL-10 ELISA Set, BD Biosciences-USA).

Cell culture to assess lymphocyte proliferation stimulated by antigen-presentation

After obtaining mononuclear cells using the Ficoll Hypaque gradient (Histopaque 1077, Sigma-USA), 3 samples of 2 x 10^6 mononuclear cells with viability above 95% were incubated for 120 hours in 96-well culture plates (Costar-USA), under humid atmosphere conditions with 5% CO_2 at 37ºC, in RPMI 1640 culture (Gibco-USA) containing 10% inactivated BFS (Gibco-USA), 2 mmol/L L-glutamine, 25 mM/L Hepes, 0.07 mM/L gentamicin and 1 x 10^5 U/L penicillin. One mg/mL of the different ELs was added to the study groups. For stimulating antigen-induced lymphocyte proliferation, 10 µg/mL of tetanus toxoid (TT) (Instituto Butantã, Brazil) were added to the culture. Twelve hours before harvesting, 5 µCi of H^3-Thymidine (Amersham Pharmacia, USA) were added. After the end of the reaction, beta counter (Packard, USA) determined the incorporation of H3-Timidine by proliferating cells.

Statistical analysis

Statistical analysis of the data regarding intensity and fluorescence percentage was performed with Friedman's test and Student-Newman-Keuls post-test, with $P \leq 0.05$.

The results obtained for lymphocyte proliferation and cytokine production were submitted to statistical analysis using analysis of variance (ANOVA) and the Student-Newman-Keuls test, with $P \leq 0.05$.

Results

Lipid profile of the monocyte/macrophage membrane and human lymphocytes treated with different lipid emulsions

Human monocytes/macrophages —PHA-activated and cultured with different LEs— presented less monounsaturated fatty acids (MUFA) and a higher PUFA concentration at the cell membrane compared to the control group cultured with no lipid emulsion added to it. In the groups cultured with fish oil lipid emulsion, there was an increase in the concentration of n-3 PUFA (docosahexaenoic acid) at the membrane of

Table II
Lipid profile of monocytes/macrophages and lymphocytes cell membrane

Fatty acids	*Control*		*SO*		*SO/FO*		*MCT/SO*		*MCT/SO/FO*		*SMOF*	
	MO	*LO*	*MO*	*LO*	*MO*	*LO*	*MO*	*LO*	*MO*	*LO*	*MO*	*LO*
Lauric (C12:0)	0.97	4	2.09	7.7	3.19	5	11.24	9.4	11.12	6	NA	6.67
Miristic (C14:0)	3.48	1.2	3.97	1.8	3.11	2.36	7.91	3.5	8.06	0.72	10.51	4.08
Palmitic (C16:0)	33.28	30.4	31.05	20.27	34.25	25.3	24.79	21.45	23.35	25.53	22.33	19.39
Estearic (C18:0)	14.56	15.72	13.54	15.01	16.33	16.09	10.52	23.18	16.64	15.31	8.95	19.83
Eicosadienoic (C20:2)	NA	NA	1.4	4.1	3.27	NA	7.64	6.5	1.11	NA	4.05	NA
Docosadienoic (C22:2)	2.39	NA	3.34	NA	NA	NA	NA	NA	1.16	NA	2.24	NA
Palmitoleic (C16:1)	2.2	NA	2.99	NA	3.68	NA	2.38	NA	NA	NA	NA	NA
Oleic (C18:1 n-9)	24.49	21.13	16.89	7.1	13.31	12.01	4.99	12.94	13.03	15.43	18.08	12
Linoleic (C18:2 n-6)	4.07	3.25	5.35	7.91	6.3	4	4.1	4.09	3.5	7.33	4.32	5.49
Gama-Linolenic (C18:3 n-6)	13.19	5.9	8.06	10.5	9.6	6.47	6.91	4.18	NA	3.53	5.05	9.9
Eicosatrienoic (C20:3 n-6)	1.37	NA	1.52	NA	NA	NA	4.1	NA	2.17	NA	NA	NA
Arakidonic (C:20:4 n-6)	NA	18.4	9.8	25.61	2.21	20.9	15.42	14.76	12.68	14.1	18.8	15.03
Alfa-Linolenic (C18:3 n-3)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Docosahexaenoic (C22:6 n-3)	NA	NA	NA	NA	4.75	3.2	NA	NA	7.18	6.59	5.67	4.5
Eicosapentaenoic (C20:5 n-3)	NA	NA	NA	NA	NA	4.67	NA	NA	NA	5.46	NA	3.11
Fatty acids groups												
Saturated Fatty acids	52.29	51.32	50.65	44.78	56.88	48.75	54.46	57.53	59.17	47.56	41.79	49.97
N-3 PUFA	NA	NA	NA	NA	4.75	7.87	NA	NA	7.18	12.05	5.67	7.61
PUFA n-6	18.63	27.55	24.73	44.02	18.11	31.37	30.53	23.03	18.35	24.96	28.17	30.42
MUFA n-9	24.49	21.13	16.89	7.1	13.31	12.01	4.99	12.94	13.03	15.43	18.08	12

Data expressed in percentage. Control = without LE; NA = not available; MO = monocytes/macrophages; LO = Lymphocytes, PUFA = polyunsaturated fatty acids, MUFA = monounsaturated fatty acids.

those cells compared to the control and all the other groups cultured without fish oil.

At the cell membrane of human lymphocytes, there was a decrease in the MUFA n-9 and saturated fatty acids and an increase in PUFA concentration, except for the MCT/SO group, which presented a reduction in n-9 MUFA, n-6 PUFA and an increase in saturated fatty acids. Fish-oil groups had an increase in n-3 PUFA (eicosapentaenoic and docosahexaenoic acids – EPA and DHA) at the cell membrane of lymphocytes compared to the control and to other groups cultured without fish oil (table II).

Effect of LEs on the expression of surface molecules

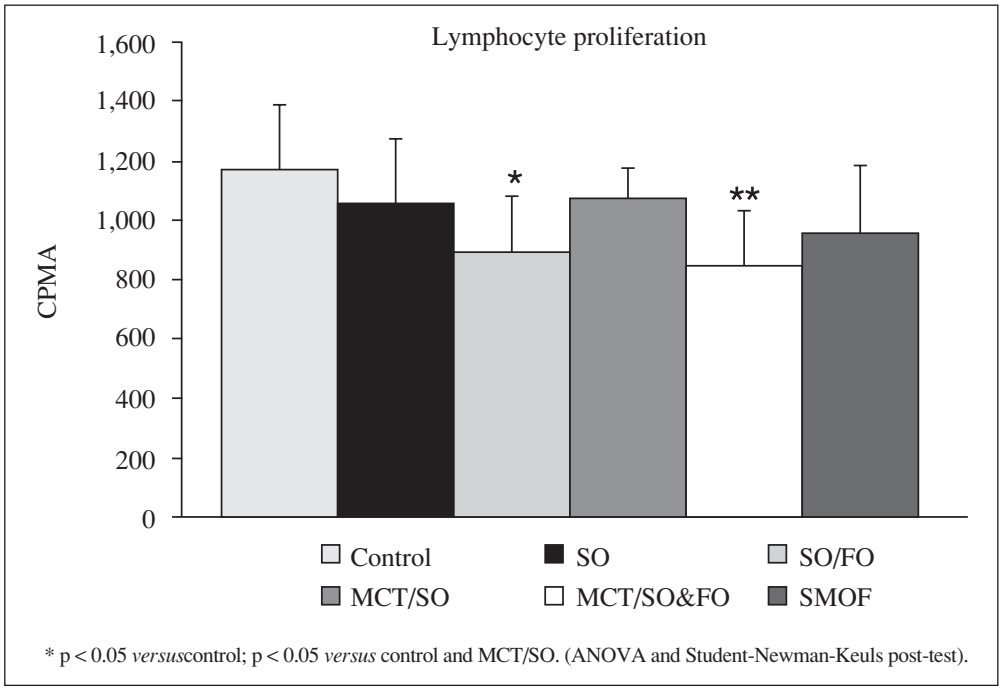
All parenteral lipid emulsions, regardless of the fatty acid content, reduced the fluorescence intensity of the antigen-presenting molecules HLA-DR expression on human monocytes/macrophages surface, and enhanced the fluorescence (%) of human T-helper lymphocytes expressing CD28 and CD152 surface molecules. The different LEs did not affect the expression of CD80 and CD86 molecules on the surface of human monocytes/macrophages (table III).

Effect of LE on lymphocytes capacity to proliferate via antigen presentation

Lipid emulsions enriched with fish oil reduced the lymphocytes' capacity to proliferate when stimulated by antigen presentation [SO/FO vs. Control ($p = 0.03$) and MCT/SO/FO *vs* Control and MCT/SO ($p = 0.001$)] (fig. 1).

Effect of different LE on cytokine production

All groups incubated with parenteral lipid emulsions reduced the production of IL-2 compared to



* p < 0.05 *versus*control; p < 0.05 *versus* control and MCT/SO. (ANOVA and Student-Newman-Keuls post-test).

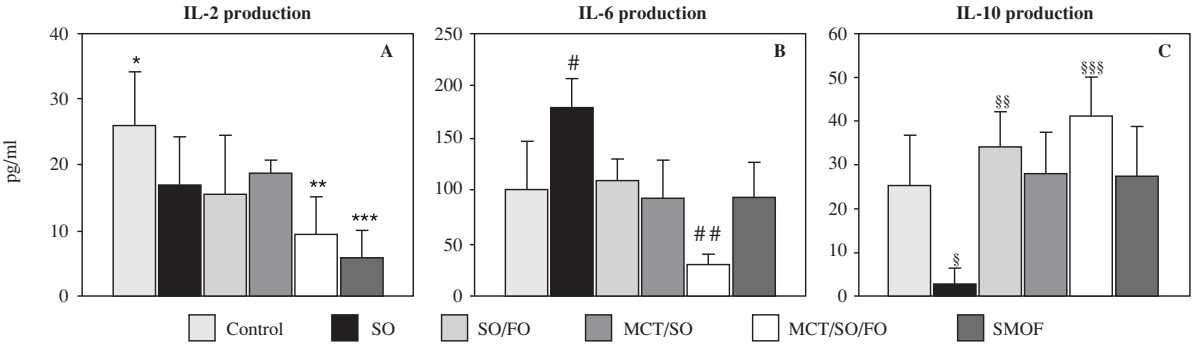
Fig. 1.—Effect of different lipid emulsion on lymphocyte proliferation.

Table III
Expression of surface molecules of human monocytes/macrophages and lymphocytes treated with different parenteral lipid emulsions

			Control	*SO*	*SO/FO*	*MCT/SO*	*MCT/SO/FO*	*SMOF*
Fluorescence (%)	*MO*	HLA-DR	98.7(a) 95.2-99.8(b)	99.1 95.2-99.9	99.2 94.6-99.8	98.3 93.4-99.8	98.1 93.1-99.9	99.4 91.9-99.9
		CD80	62.6 35.5-76	67.7 34.1-76.1	75 36.1-81	57.2 27-66.9	62.5 25.2-78.4	63.8 29.3-71.7
		CD86	84.2 80-98.4	82.8 68.8-96.3	85.6 69.6-94.1	83 80.8-95.2	81.3 72.6-94.7	81.6 72.5-97.7
	LO	CD 28	82.8 81.3-88.6	90.9* 81-94.1	90.4* 83.3-92.5	91.5* 85.1-94.4	92.6* 82.3-95.6	90.1* 85.6-94.7
		CD152	54.4 50.4-77.6	52.9 46.1-70.2	55.4 49.7-67.3	61.3 50.1-76.2	61.3 53.5-75.3	54.4 48.3-76.9
Fluorescence Intensity (%)	*MO*	HLA-DR	100 100-100	87.6* 80.8-92.3	84* 76.2-90.5	81* 79.5-96	85* 77.3-95.8	80* 74.1-94.3
		CD80	100 100-100	103.2 90.5-119.6	88.3 79.3-94.3	97.2 84.9-115.6	103.5 78.1-119.6	89 83.3-114.5
		CD86	100 100-100	94.2 92.8-118	96.9 66.3-112.5	94.9 80.2-126.7	91.3 79.2-127	88.6 77.9-126.9
	LO	CD 28	100 100-100	91.5 85.9-102.2	97.3 92.2-101.4	94.9 89.1-101.3	96.9 92.9-103.8	95.2 89.1-99
		CD152	100 100-100	120.6* 111.8-145.6	108.8* 104.8-133.1	127.7* 110.2-145.7	114.6* 109.8-124.6	121.3* 112.7-133.6

Results expressed as (a) median (b) 25-75 percentile. * p < 0.05 *versus* Control, (Friedman Test and Student-Newman-Keuls test). n = 10. Abbreviations: MO = monocytes/macrophages, LO = lymphocytes.

the control group (no lipid emulsion). The MCT/SO group presented the lowest reduction of IL-2, whereas the SMOF group presented the highest inhibition rate of cytokine production (SMOF vs. SO, SO/FO, MCT/SO and Control group. p < 0.01) (fig. 2).



(A): * p < 0.02 *vs* all LE; ** p < 0.03 *vs* SO, SO/FO and MCT/SO; *** p < 0.01 *vs* all groups.
(B): # p < 0.001 *vs* all groups; # # p < 0.001 *vs* all groups.
(C): § p < 0.001 *vs* all groups; §§ p = 0.03 *vs* control; §§§ p < 0.01 *vs* control, MCT/SO and SMOF (ANOVA and Student Newman Keuls).

Fig. 2.—In vitro effect of different parenteral LE on cytokines production.

The SO group increased the production of IL-6 in contrast to the control and all the groups treated with LEs ($p < 0.001$). The lowest production of IL-6 was observed in the MCT/SO/FO group ($p < 0.001$) (fig. 2).

Production of the anti-inflammatory cytokine IL-10 decreased in the SO group when compared to the other groups ($p < 0.05$). However, the production of IL-10 increased in the SO/FO and MCT/SO/FO groups compared to the control group ($p < 0.05$) and to groups with no fish oil added: SO and MCT/SO ($p < 0.05$) as well as to the SMOF group (fig. 2).

Discussion

In the current study we observed an increased incorporation of PUFA, particularly from the n-3 series, at the membrane of monocytes/macrophages and activated lymphocytes when they were cultured with LEs containing fish oil (SO/FO, MCT/SO/FO and SMOF groups). We also found a decrease in n-9 MUFA (oleic acid). Our finding agrees to previous studies where mitogen-activated mononuclear cells cultured with PUFA increased PUFA incorporation at the cell membrane and reduced the concentration of saturated and monounsaturated fatty acids.[23,24]

The increased incorporation of polyunsaturated fatty acids (PUFA) at the cell membrane enhances its fluidity and consequently the expression of surface molecules of immunological cells. On the other hand, the decrease in PUFA at the membrane and the increase in MUFA and saturated fatty acids decrease membrane fluidity, which can decrease the expression of surface molecules.[20-22] Keratinocytes cultured with EPA and arachidonic acid (AA) enhanced the expression of ICAM-1. This finding was associated to the increased fluidity of the cell membrane of keratinocytes after the incorporation of n-3 and n-6 PUFA.[22]

Theoretically, the change of fatty acid profile, at the cell membrane observed in the current study, should favor the expression of surface molecules. However, the response of surface molecules expression in this study was not consistent to former findings with regard to the lipids emulsions they have been exposed to.

In the present observation, all parenteral lipid emulsions decreased the expression of HLA-DR molecules on activated monocytes/macrophages surface. Regarding containing-fish oil LE groups, and consistent with our findings, Hughes et al. found that activation of human mononuclear cells by INF-gamma and subsequent incubation with EPA and DHA, (using the same ratio naturally found in fish oil), reduced the expression of surface molecules - HLA-DR, HLA-DP and HLA- DQ. They also found a reduction in lymphocyte proliferation after antigen stimulation with the tetanus toxoid antigen.[25,26]

In the present *in vitro* study, there was an increase in lymphocyte receptors for the co-stimulatory molecules CD28 and CD152 by all studied lipid emulsions. Regarding containing-fish oil groups, Sasaki et al. had also found enhanced expression of CD28 molecules on the surface of T-lymphocytes in isogenic C57BL/6 mice fed with an oral diet supplemented with n-3 PUFA.[21] In the other hand, mice fed with EPA and DHA did not change the expression of CD28, but EPA enhanced the expression of CD152 compared to control animals fed with corn oil, rich in n-6 PUFA. The authors found a decrease in the proliferation of lymphocytes stimulated by antibodies anti-CD3 and anti-CD28 with EPA, suggesting that EPA could inhibit the proliferation of lymphocytes by enhancing the molecule that downregulates the co-stimulatory signal (CD152).[27]

In the present study, reduced lymphocyte proliferation could be expected for all groups incubated with LEs due to the increased expression of CD152 and reduced production of IL-2, a cytokine witch stimulate lymphocyte proliferation.[28,29] However, there was a decreased lymphocyte proliferation only in the groups that received fish oil-based lipid emulsions (SO/FO

and MCT/SO/FO). In addition, although SMOF contain fish oil group and had a lower production of IL-2, this parenteral lipid emulsion did not significantly decrease lymphocyte proliferation, indicating a favorable effect of this fish oil-containing lipid emulsion on this variable.

Potential mechanisms that can be involved in the fish oil-related modulation of lymphocyte proliferation include inhibition of cell cycle progression and induction of apoptosis. Jurkat cells incubated with EPA and DHA had reduced lymphocyte proliferation and also inhibited the MAP-kinase signaling pathway, which plays a key role in the progression of the cell cycle during lymphocyte proliferation.[30,31] In another *in vitro* study, EPA and DHA increased the number of lymphocytes in the G0/G1 phase and reduced the ratio of these cells at phases S and G2/M of the cell cycle, confirming that reduced lymphocyte proliferation could be due to inhibition of cell cycle progression.[32] In addition, an *in vitro* study has shown that there is a relationship between the inhibition of lymphocyte proliferation and the pro-apoptotic effect of n-3 PUFA. Incubation with DHA reduced the proliferation of HL-60 cells.[33]

In vitro studies with lipid emulsion added to the culture media have shown that mechanisms that trigger apoptosis can be activated by the deposit of free radicals in the cell since PUFA are more susceptible to lipid peroxidation.[34] The increase in the concentration of free radicals in cell cultures can induce death and affect the cell cytoskeletal structure.[35]

This latest observation allows us to speculate that in our study the potential inhibitory effect of lymphocyte proliferation found in the experimental mixtures with LEs containing fish oil, except for the new SMOF emulsion, could have been associated with the increased oxidative stress. Although the SMOF group contains fish oil, it is worth emphasizing that this parenteral lipid emulsion has the highest antioxidant content (0.2 g/L) compared to the other groups (approximately 0.1 g/L).

In our study, the experimental mixture of MCT/SO with fish oil emulsion (4:1) had promoted an anti-inflammatory effect, with downregulation of the pro-inflammatory cytokine IL-6 and upregulation of the anti-inflammatory IL-10. Additionally, the experimental mixture of SO with fish oil (4:1) also increased IL-10.

Regarding the differences between *in vitro* and *in vivo* studies, especially in studies involving cytokines, our findings also agrees with previous scientific reports of n-3 PUFA which have shown, after an inflammatory stimulus, a decreased production of pro-inflammatory cytokines such as IL-1-alfa and beta, IL-6 and TNF-alpha and beta.[36-38]

During parenteral supply of fish oil, n-3 PUFA can become quickly available to organs, tissues and immune system cells, expediting its modulating effect. In this sense, the infusion of fish-oil based lipid emulsion in healthy volunteers for a short period of time (48 hours) significantly increased the ratio of n-3/n-6 fatty acids at the plasma and at the monocyte membrane and reduced the production of pro-inflammatory cytokines, TNF-alpha, IL-1, IL-6 and IL-8, after stimulation of monocytes with endotoxin. This effect was not observed in the control group, which received the infusion of soybean oil-based LE.[39] Clinically, the preoperative parenteral infusion of fish oil-based lipid emulsion in surgical patients also reduced the amount of IL-6.[40]

In our *in vitro* study, the soybean oil-based lipid emulsion, rich in n-6 PUFA, increased the pro-inflammatory cytokine IL-6 and reduced the anti-inflammatory cytokine IL-10 in the supernatant of cell cultures. The inflammatory effect of a lipid emulsion rich in n-6 PUFA was also observed in animals with burns, fed with central parenteral nutrition, in which the sunflower oil infusion increased the plasma levels of IL-6 compared to control animals that received no fat in their parenteral nutrition.[41] Clinically, the parenteral infusion of the lipid emulsion containing soybean oil in severely stressed surgical patients resulted in increased serum IL-6 compared to the control group that received parenteral nutrition without soybean oil.[42]

It is interesting to observe that SMOF had a neutral effect on the production of IL-6 and IL-10, although it contains fish oil. Considering that the mixture of MCT/SO with fish oil reduced the level of IL-6 and amplified IL-10, the neutral effect of SMOF could be attributed to the amount of olive oil (25%), rich in n-9 monounsaturated fatty acids. The n-3, n-6 PUFA and n-9 MUFA are incorporated by the cell membranes, but their affinity decreases in the order mentioned.[432] We could presume that the increased availability of n-9 affected the incorporation of the n-3 and n-6 series, because the ratio n-6:n-3 is higher at the membrane of monocytes/macrophages and lymphocytes from the SMOF group compared to the MCT/SO/FO group (SMOF = 7:1.4 and MCT/SO/FO = 3.8:1 at the membrane of monocytes/macrophages and SMOF = 4:1 and MCT/SO/FO= 2:1 at the membrane of lymphocytes).

The reduced production of pro-inflammatory cytokines IL-2 and IL-6 and the increase of anti-inflammatory cytokine IL-10 observed with fish oil LE could be of clinical importance as it can modulate the inflammatory response and reduce its severity.

Conclusions

Based on the findings of our study with activated human monocytes/macrophages and lymphocytes, we can conclude that parenteral lipid emulsions, regardless of their fatty acid composition, are responsible for similar modulation of the expression of surface molecules involved in the process of antigen presentation, although this modulation varies depending on the type of cells studied. Adding 20% of fish oil emulsion to convention lipid emulsions containing soybean oil and MCT/soybean oil results in anti-inflammatory effect related to cytokine production and decreased lymp-

hocyte proliferation. The new lipid emulsion —SMOF— containing a mixture of soybean, olive and fish oil, plus medium-chain triglycerides, had a neutral impact on the studied immune and inflammatory variables.

Acknowledgment

This work was supported by research grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (Fapesp-04/04225-8) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-505633/04-3). The authors thank Fresenius-Kabi for kindly concede the lipid emulsions.

References

1. Lacetera N, Scalia D, Mashek DG, Bernabucci U, Grummer RR. Effects of intravenous triacylglycerol emulsions on lymphocyte responses to mitogens in fasted dairy cows undergoing intense lipomobilization. *J Dairy Res* 2007; 74: 323-8.
2. De Pablo MA & de Cienfuegos A. Modulatory effects of dietary lipids on immune system functions. *Immunol Cell Biol* 2000; 78: 31-39.
3. Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr* 2002; 56: S14- S19.
4. Campos FG, Waitzberg DL, Habr-Gama A, Logullo AF, Noronha IL, Jancar S, Torrinhas RS, Furst P. Impact of parenteral n-3 fatty acids on experimental acute colitis. *Br J Nutr* 2002; 87: S83-8.
5. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. *JPEN J Parenter Enteral Nutr* 2006; 30: 351-67.
6. Waitzberg DL, Bellinati-Pires R, Yamaguchi N, Massili-Oku S, Salgado MM, Hypolito IP, Soares SC, Goncalves EL, Furst P. Influence of medium-chain triglyceride-based lipid emulsion on rat polymorphonuclear cell functions. *Nutrition* 1996; 12: 93-9.
7. Waitzberg DL, Lotierzo PH, Logullo AF, Torrinhas RS, Pereira CC, Meier R. Parenteral lipid emulsions and phagocytic systems. *Br J Nutr* 2002; 87: S49-57.
8. Appleman LJ, Boussiotis VA. T cell anergy and costimulation. *Immunol Rev* 2003; 192: 161-80.
9. Granucci F, Zanoni I, Feau S, Ricciardi-Castagnoli P. Dendritic cell regulation of immune responses: a new role for interleukin 2 at the intersection of innate and adaptive immunity. *EMBO J* 2003; 22: 2546-51.
10. Grose RH, Howarth GS, Xian CJ, Hohmann AW. Expression of B7 costimulatory molecules by cells infiltrating the colon in experimental colitis induced by oral dextran sulfate sodium in the mouse. *J Gastroenterol Hepatol* 2001; 16: 1228-34.
11. Greenfield EA, Nguyen KA, Kuchroo VK. CD28/B7 costimulation: a review. *Crit Rev Immunol* 1998; 18: 389-418.
12. Slavik JM, Hutchcroft JE, Bierer BE. CD28/CTLA-4 and CD80/CD86 families: signaling and function. *Immunol Res* 1999; 19 (1): 1-24.
13. McCoy KD, Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. *Immunol Cell Biol* 1999; 77: 1-10.
14. Vandenborre K, Van Gool SW, Kasran A, Ceuppens JL, Boogaerts MA, Vandenberghe P. Interaction of CTLA-4 (CD152) with CD80 or CD86 inhibits human T-cell activation. *Immunology* 1999; 98 (3): 413-21.
15. Grimm H, Mertes N, Goeters C et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006; 45: 55-60.
16. Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, Koch T. Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006; 34: 972-9.
17. Wichmann NW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effect of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med* 2007; 35: 700-6.
18. Brill A, Baram D, Sela U, Salamon P, Mekori YA, Hershkoviz R. Induction of mast cell interactions with blood vessel wall components by direct contact with intact T cells or T cell membranes in vitro. *Clin Exp Allergy* 2004; 34: 1725-31.
19. Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem* 1957; 226: 497-509.
20. Calder PC, Yaqoob P, Harvey DJ, Watts A, Newsholme EA. Incorporation of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty acid composition and membrane fluidity. *Biochem J* 1994; 300: 509-18.
21. Sasaki T, Kanke Y, Kudoh K, Misawa Y, Shimizu J, Takita T. Effects of dietary docosahexaenoic acid on surface molecules involved in T cell proliferation. *Biochim Biophys Acta* 1999; 1436: 519-30.
22. Lu L, Okada N, Nakatani S, Yoshikawa K. Eicosapentaenoic acid-induced changes in membrane fluidity and cell adhesion molecules in cultured human keratinocytes. *Br J Dermatol* 1995; 133: 217-22.
23. Ferber E, De Pasquale GG, Resch K. Phospholipid metabolism of stimulated lymphocytes. Composition of phospholipid fatty acids. *Biochim Biophys Acta* 1975; 398 (3): 364-76.
24. Rode HN, Szamel M, Schneider S, Resch K. Phospholipid metabolism of stimulated lymphocytes. Preferential incorporation of polyunsaturated fatty acids into plasma membrane phospholipid upon stimulation with concanavalin A. *Biochim Biophys Acta* 1982; 688: 66-74.
25. Hughes DA, Pinder AC. n-3 polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes. *Am J Clin Nutr* 2000; 71: 357S-60S.
26. Hughes DA, Pinder AC. N-3 polyunsaturated fatty acids modulate the expression of functionally associated molecules on human monocytes and inhibit antigen-presentation *in vitro*. *Clin Exp Immunol* 1997; 110: 516-23.
27. Ly LH, Smith R, Switzer KC, Chapkin RS, McMurray DN. Dietary eicosapentaenoic acid modulates CTLA-4 expression in murine CD4+ T-cells. Prostaglandins Leukot. Essent. *Fatty Acids* 2006; 74: 29-37.
28. Nelson BH. IL-2, regulatory T cells, and tolerance. *J Immunol* 2004; 172: 3983-8.
29. Waldmann TA. The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. *Nat Rev Immunol* 2006; 6: 595-601.
30. Denys A, Hichami A, Khan NA. Eicosapentaenoic acid and docosahexaenoic acid modulate MAP kinase (ERK1/ERK2) signaling in human T cells. *J Lipid Res* 2001; 42: 2015-20.
31. Denys A, Hichami A, Khan NA. Eicosapentaenoic acid and docosahexaenoic acid modulate MAP kinase enzyme activity in human T-cells. *Mol Cell Biochem* 2002; 232: 143-8.
32. Gorjão R, Cury-Boaventura MF, de Lima TM, Curi R. Regulation of human lymphocyte proliferation by fatty acids. *Cell Biochem Funct* 2007; 25: 305-15.
33. Lawrence C, Chiu M, Elaine Y, Wong L, Vicent EC. Docosahexaenoic acid modulates different genes in cell cycle and apoptosis to control growth of human leukemia HL-60 cells. *Int J Oncol* 2004; 25: 737-44.
34. Muhlebach SF, Steger PJ. Lipid peroxidation of intravenous fat emulsions: a pharmaceutical issue with clinical impact? *Nutrition* 1998; 14: 720-1.
35. Bellomo G, Mirabelli F. Oxidative stress injury studied in isolated intact cells. *Mol Toxicol* 1987; 1 (4): 281-93.
36. Endres S, Ghorbani R, Kelley VE et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of IL-1 and TNF alpha by mononuclear cells. *N Engl J Med* 1989; 320: 226-71.
37. Endres S, Meydani S N, Dinarello C A. Effects of omega 3 fatty acid supplements on ex vivo synthesis of cytokines in human

volunteers. Comparison with oral aspirin and ibuprofen. *World Rev Nutr Diet* 1991; 66: 401-6.
38. Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr* 1996; 63: 116-22.
39. Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, Grimminger F, Seeger W. Short-Time Infusion of Fish Oil-Based Lipid Emulsions, Approved for Parenteral Nutrition, Reduces Monocyte Proinflammatory Cytokine Generation and Adhesive Interaction with Endothelium in Humans. *The Journal of Immunology* 2003; 171: 4837-43.
40. Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative administration of n-3 fatty acids. *Br J Nutr* 2002; 87: S89-S94.
41. Hayashi N, Tashiro T, Yamamori H, Takagi K, Morishima Y, Otsubo Y, Sugiura T, Furukawa K, Nitta H, Nakajima N, Suzuki N, Ito I. Effects of intravenous omega-3 and omega-6 fat emulsion on cytokine production and delayed type hypersensitivity in burned rats receiving total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1998; 22 (6): 363-7.
42. Furukawa K, Yamamori H, Takagi K, Hayashi N, Suzuki R, Nakajima N, Tashiro T. Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition* 2002; 18: 235-40.
43. Chan S, McCowen KC, Bistrian B. Medium-chain triglyceride and n-3 polyunsaturated fatty acid-containing emulsions in intravenous nutrition. *Curr Opin Clin Nutr Metab Care* 1998; 1: 163-9.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):297-303
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Radiomodifying effect of organic grape juice supplementation on hematological parameters and organ weight in whole-body X-irradiation in rats

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Abstract

The aim of this study is testing black grape juice as a radiomodifier against whole body X-irradiation using an animal model. Sixteen male Wistar rats were divided into four groups where two were irradiated by X-rays from a 200 kV machine specially designed to biological samples. Animals were fed ad libitum and drank voluntarily 2-10 ml a day of grape juice or placebo (isocaloric glucose and fructose solution) for one week before and two weeks after 6 Gy X-irradiation when they were sacrificed. Results have shown a significant liver weight loss in irradiated placebo group only while grape juice one has presented no losses. Hematological analysis showed typical abnormalities for ionizing radiation exposure, including early leucopenia and anemia. The intake of grape juice induced an increase in granulocyte percent count.

(*Nutr Hosp*. 2009;24:297-303)

Key words: *X-rays. Black grape juice. Radiomodifier. Rats.*

EFECTO RADIOMODIFICADOR DE LA SUPLEMENTACIÓN CON MOSTO DE UVA DE CULTIVO ECOLÓGICO SOBRE PARÁMETROS HEMATOLÓGICOS Y PESO DE ÓRGANOS EN RATAS SOMETIDAS A IRRADIACIÓN DE CUERPO ENTERO CON RAYOS X

Resumen

El propósito de este estudio fue comprobar el efecto radiomodificador del mosto tinto de uva frente a irradiación de cuerpo entero con rayos X usando un modelo animal. Dieciséis ratas macho de raza Wistar fueron irradiadas mediante un aparato de 200 kV diseñado específicamente para muestras biológicas. Los animales fueron alimentados ad libitum y bebieron cada dia voluntariamente entre 2 y 10 ml de mosto de uva o placebo (solución isocalórica de glucosa y fructosa) durante una semana antes y dos semanas después de irradiación con rayos X a una dosis de 6 Gy, momento en que fueron sacrificadas. Los resultados mostraron una pérdida significativa de peso hepático en los animales irradiados tratados con placebo, mientras que los tratados con mosto presentaron valores similares a los controles no irradiados. El análisis hematológico presentó las anomalías típicas de la exposición a radiación ionizante, con disminución leucocitaria temprana y anemia. La ingestión de mosto de uva indujo un aumento del porcentaje de granulocitos.

(*Nutr Hosp*. 2009;24:297-303)

Palabras clave: *Rayos X. Mosto tinto de uva. Radiomodificador. Ratas.*

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Recibido: 5-II-2009.
Aceptado: 6-III-2009.

Introduction

The use of ionizing radiation for a wide range of purposes has been growing up rapidly since the nuclear holocaust. Nuclear and radiological technologies have spread over most of knowledge fields, from Engineering to Health Sciences, even though its uses can be controversial and a bottleneck on radiation protection is a problem to be solved. Exposure to ionizing radiation can be harmful and searching for radiomodifiers (drugs or nutrients) has full epidemiological relevance. The ideal radioprotective agent (radiomodifier) must provide: a) significant protection against radiation effects; b) a general protective effects to all other organs including non-target ones (in case of therapy); c) acceptable route of administration (oral is preferred); d) low toxicity; e) compatibility for use with other drugs.[1,2] Radiomodifiers are substances able to reduce the effect of the ionizing radiation strike, but unable to stop it. Their action is neither like a barrier nor shielding for ionizing radiation, but as scavengers for reactive oxygen species. Clinically relevant radiomodifier substances should have low or none toxicity and synergic action with other drugs. Dealing with these purposes the best option is a functional food or nutraceutical. Unfortunately, there is no compound that manifest all these properties at a time and among more than 300 radiomodifiers developed,[2] amifostine (WR2721, Ethyol) has proved as most efficient but only authorized for radiotherapy treatment of head and neck cancer.[3,4] Natural compounds in human diet could provide functional antioxidants, such as vitamins, minerals and enzymes acting as radiomodifiers on reducing oxidation damage caused by ionizing radiation exposure. An example is the use of vitamin E for recovering post-irradiation procedures showing good results.[5-7] Radiation exposure might be heterogeneous in terms of dose, dose rate and quality, depending on the type of the radiation source released and the location of the subject on site. Therefore, methods are needed to protect against and treat a wide range of early and later developing radiation-induced injuries. Acute effects of the exposure to ionizing radiation mainly include immune suppression, hematopoietic cell loss, mucosal damage, and potential injury to other sites such as lung, kidney, liver and central nervous system.[8] Liver plays a particular role in radiosensitivity and as a consequence of its redundant, parallel functional structure, liver is able to deal with high radiation dose as long as only partial irradiation occurs; otherwise, whole organ irradiation leads to hepatocyte failure and RILD (Radiation Induced Liver Disease) such as hepatitis might be installed.[9]

Long-term effects include dysfunction, fibrosis and cancer in a wide range of organs and tissues. Blood counts can help to manage the decision-making process in clinical decisions. The hematopoietic syndrome is significantly important to partial-body or whole-body ionizing radiation exposures exceeding 1Gy.[10] Irradiation of bone marrow stem and progenitor cells at increasing doses results in exponential cellular death.[10] Mitotically active hematopoietic progenitors have a limited capacity to divide after a whole-body radiation dose greater than 2 or 3 Gy.[11] After exposure, a hematologic crisis might lead to: a) predisposition to infection, b) bleeding, and c) poor wound healing, among others. A predictable decline in lymphocytes occurs after irradiation, and in fact, there is a 50% decline in absolute lymphocyte count within the first 24 hours after exposure, followed by a further, more severe decline within 48 hours.[12] The predictability of the rate of lymphocytic depletion count, which characterizes a potentially lethal exposure, has led to the development of a model using lymphocyte depletion kinetics (Andrew's curve) as a biodosimetric tool.[12-14] The rate of decline of the absolute lymphocyte count over the initial 12 hours and for a week after exposure is a function of cumulative dose[15] and the lymphocyte depletion kinetics predicts dose assessment for a photon-equivalent dose range within 1 and 10 Gy, range in which most of the radiobiological effects take place. For an optimal screening and a good support for clinical decision-making process a complete blood cell count with leukocyte differential should be obtained immediately after exposure, 3 times per day for the next 2 to 3 days, and then twice per day for the following 3 to 6 days. However, it is recommended at least 3 complete blood counts with differential within the initial 4 days after exposure to calculate a slope for lymphocyte decline for estimating the exposure dose. The onset of other cytopenias varies depending on both dose and dose rate and granulocyte counts may transiently increase before decreasing in exposures less than 5 Gy in humans.[16] This behavior, termed an *abortive rise,* is a transient increase in the absolute number of cells in any compartment of a nearly depleted hematopoietic cell renewal system, and may indicate a survivable exposure.[16]

The probability of occurrence of those effects can be minimized or altered by the radiomodifier action. Several evidences suggest that grape juice and seeds can provide protection levels against exposure to ionizing radiation.[17] Radiobiological effects of ionizing radiation are a brand new issue of Science and have been taking noticeable advances over the last 60 years.[18] However, most of the effort made has been facing a hard pathway, bordering other fields such as Biochemistry, Molecular Biology and Medicine, which turns Radiobiology out a complex field to be explored.

The present work is aimed to test black grape juice as a radiomodifier against whole body X-irradiation using rats as an animal model in order to assess the possible changes in bodily and hematological parameters.

Materials and Methods

Animals

Sixteen male Wistar rats weighing 200-250 g (Harlan, Barcelona, Spain), housed at the animal house of University of León (Spain), were included in the study. The experimental protocol used was approved by the

University of León Ethical Committee, and adhered to the European Community Guiding Principles for the Care and Use of Animals.

Whole Body Irradiation

Animals were divided into four groups: (MN) non-irradiated, grape juice supplemented; (GN) non-irradiated, placebo (isocaloric glucose plus fructose) supplemented; (MR) irradiated, grape juice supplemented, and (GR) irradiated, placebo (isocaloric glucose/fructose solution) supplemented. In order to immobilize the animals, anesthesia was induced by intraperitoneal administration of pentobarbital 0.6% in saline (10 ml/kg body weight), at noon, 15 minutes before irradiation, ensuring the loss of palpebral and plantar reflex activity and spontaneous respiration throughout the procedure. The animals were placed in decubitus pronus on a plexiglas board, so that four animals would be irradiated at a time and exposed to a single dose of 6 Gy of whole body X-irradiation from an X-ray machine (200 kV) MAXISHOT 200 (YXLON, Copenhagen, Denmark), at a radiation dose rate of 0.40 Gy/min, with a source-skin distance (SSD) of 50 cm.

Food and Drink

Animals were fed according to a standard rat chow diet, having free access to *ad libitum* water and food. After one week adaptation to individual cages, they were allowed to ingest a maximum of 10 ml of test compound (grape juice) or placebo, depending on their assigned group. Environmental conditions were controlled (12-hour photoperiod and 20 ± 2 °C) throughout the experimental period.

Grape juice and placebo composition

Ecologically-produced (organic) black grape juice was obtained from the city of Garibaldi (Rio Grande do Sul, Brazil), in the main grape-growing region of the state. Grapes were cultivated in 2007 and the juice was prepared the same year. The concentration (mg/L) of phenolic compounds in the grape juice was determined as follows: Resveratrol 3.95 ± 0.01, Quercetin 8.95 ± 0.09, Rutin 3.75 ± 0.03, Gallic acid 81.07 ± 2.03, Caffeic acid 30.28 ± 2.00, Flavonoids 0.249 ± 0.002.[19] Placebo solution was made using an equimolar mixture of glucose and fructose to be isocaloric with the sugar composition in the grape juice (95 g/L).

Blood samples collection

Blood samples were collected at 6, 24, 48 hours and 16 days following X-ray exposure using heparinized capillaries by puncturing the retro-orbital plexus after prior mild anesthesia with isofluoran.

Table I
White cell counts obtained at 6, 24, 48 hours, and 16 days after whole-body X-irradiation of 6 Gy in male Wistar rats

Time/Group		*Leukocytes (x 10^9/L)*	*Lymphocytes (x 10^9/L)*	*Monocytes (x 10^9/L)*	*Granulocytes (x 10^9/L)*
6 h	MN	8.21 ± 0.82	4.76 ± 0.94	0.25 ± 0.08	3.20 ± 0.69
	MR	**3.62 ± 0.59***#	**1.00 ± 0.27***#	0.25 ± 0.06	2.40 ± 0.33
	GR	**4.19 ± 0.97***#	**1.39 ± 0.39***#	0.25 ± 0.06	2.54 ± 0.62
	GN	9.22 ± 1.45	6.46 ± 1.42	0.24 ± 0.11	2.52 ± 0.16
24 h	MN	9.1 ± 0.96	7.12 ± 0.78	0.24 ± 0.06	1.76 ± 0.38
	MR	**1.1 ± 0.08***#	**0.25 ± 0.03***#	**0.10 ± 0.01***#	**0.73 ± 0.07***#
	GR	**0.7 ± 0.12***#	**0.18 ± 0.05***#	**0.06 ± 0.01***#	**0.48 ± 0.06***#
	GN	10.2 ± 1.78	8.24 ± 1.52	0.28 ± 0.02	1.71 ± 0.66
48 h	MN	9.34 ± 1.41	8.07 ± 1.16	0.11 ± 0.03	1.16 ± 0.26
	MR	**0.55 ± 0.04***#	**0.11 ± 0.01***#	**0.04 ± 0.01**#	**0.40 ± 0.04***#
	GR	**0.81 ± 0.32***#	**0.39 ± 0.18***#	**0.06 ± 0.04**#	**0.37 ± 0.11***#
	GN	7.37 ± 0.84	**5.78 ± 0.54***	**0.33 ± 0.13***	1.27 ± 0.41
16 d	MN	3.22 ± 0.47	2.38 ± 0.68	0.03 ± 0.01	0.81 ± 0.31
	MR	**0.67 ± 0.09***#	**0.50 ± 0.07***#	0.02 ± 0.01	**0.14 ± 0.03***#
	GR	**0.46 ± 0.12***#	**0.40 ± 0.05***#	0.02 ± 0.01	**0.15 ± 0.07***#
	GN	3.68 ± 0.39	2.84 ± 0.27	**0.09 ± 0.03***	0.75 ± 0.20

MN (grape juice only), MR (grape juice + X-irradiation), GR (placebo + X-irradiation) and GN (placebo only).
Means ± s.e.m. of 4 animals per group. Significant differences from non-irradiated groups at $p < 0.05$ (Newman-Keuls test) are indicated as *(MN) and #(GN).

Table II
Relative (%) hematological parameters obtained at 6, 24, 48 hours, and 16 days after whole-body X-irradiation of 6 Gy in male Wistar rats

Time/Group		*Lymphocyte (%)*	*Monocyte (%)*	*Granulocyte (%)*
6 h	MN	57.0 ± 9.8	2.85 ± 0.76	40.1 ± 10.3
	MR	**26.2 ± 5.5***#	**6.45 ± 0.66***#	**67.3 ± 11.6***#
	GR	**32.4 ± 2.0***#	**7.15 ± 1.88***#	**60.5 ± 3.9***#
	GN	68.4 ± 4.2	2.95 ± 1.29	28.7 ± 6.2
24 h	MN	78.3 ± 3.7	2.67 ± 0.54	19.0 ± 3.2
	MR	**23.0 ± 2.9***#	**8.97 ± 0.85***#	**68.0 ± 3.2***#
	GR	**22.0 ± 5.2***#	**8.32 ± 0.80***#	**69.7 ± 5.3***#
	GN	80.5 ± 4.0	3.13 ± 0.78	16.3 ± 4.14
48 h	MN	86.8 ± 1.4	1.18 ± 0.33	12.0 ± 1.26
	MR	**19.9 ± 1.3***#	**7.58 ± 1.46***#	**72.5 ± 1.9***#
	GR	**42.4 ± 7.3***#	**5.60 ± 1.40***#	**52.0 ± 7.5***#
	GN	79.3 ± 4.8	4.30 ± 1.26	16.4 ± 3.6
16 d	MN	69.3 ± 15.7	2.82 ± 0.22	29.9 ± 15.9
	MR	75.6 ± 2.7	3.23 ± 1.10	21.2 ± 2.0
	GR	72.2 ± 8.5	3.50 ± 1.20	24.4 ± 7.3
	GN	77.7 ± 3.9	2.55 ± 0.62	19.8 ± 3.5

MN (grape juice only), MR (grape juice + X-irradiation), GR (placebo + X-irradiation) and GN (placebo only).
Means ± s.e.m. of 4 animals per group. Significant differences from non-irradiated groups at $p < 0.05$ (Newman-Keuls test) are indicated as *(MN) and #(GN).

Results and discussion

As it can be seen in table I, leukocyte count decreased with significant differences for all samples considering MR and GR groups in relation to controls. Lymphocyte counts fell down dramatically, but they showed a relative recovery for MR group, not seen in GR. This fall in lymphocyte counts may be interrupted by an abortive rise[16] followed by final recovery due to the release of damaged blood cells. Monocyte count dropped significantly in comparison to controls only for 24 and 48 hours. Granulocytes decreased, for all sampling times and groups. Erythrocyte count (table III) showed normal values for the first 48 hours and a significant decrease at 16 days after irradiation, indicative that an anemia was installed. Levels of hemoglobin decreased significantly at 48 hours for MR group, and at 16 days in MR and GR, respectively to controls. Although there is absence of statistical significance on hemoglobin levels for MR and GR groups compared each other, at 16 days there is a tendency on keeping higher values for MR group, with higher variability found on GR group. This tendency could be related to the glucose and fructose absorption decrease in small intestine in irradiated rats, with increase in CO_2 production in peripheral blood leading to an increase of hemoglobin concentration.[20, 21]

Changes in hemoglobin and erythrocyte count are also to be expected after significant damage to bone marrow subsequent to X-irradiation, as shown in a number of studies.[22,23] At this respect, hematocrit values were statistically distinguishable for groups MR and GR with respect to controls only at 16 days. Platelet counts have shown statistical significances for MR and GR only for 16 days respectively to controls. Two animals from GR group showed nasal bleeding possibly related to platelet depletion, in contrast to MR group where no bleeding was noticed over the experimental period. Relative counts (%) for lymphocytes (table II), were significantly decreased for MR and GR respectively to controls for 6, 24 and 48 hours but not for 16 days. However, percent counts for monocytes and granulocytes increased at 6, 24 and 48 hours relative to controls. When comparing the X-irradiated groups at 6 and 48 hours post-irradiation, total leukocyte count was higher for GR than MR group (table I). However, the much higher variability appearing in the data from GR group indicates that some caution has to be taken when discarding possible radioprotective effects of grape juice. Percent lymphocyte count was higher on GR than MR, but percent granulocyte count was higher on MR than GR group, which suggest a real possibility of recovering from damaged bone marrow, in agreement with the proposed radioprotective effect of grape juice supplementation over bone marrow. All in all, these results point to massive bone marrow damage as a consequence of whole-body acute X-irradiation, and further experiments should be carried out at different times post-irradiation with direct bone marrow sampling[23] to clarify the time course of these radiomodifying effects.

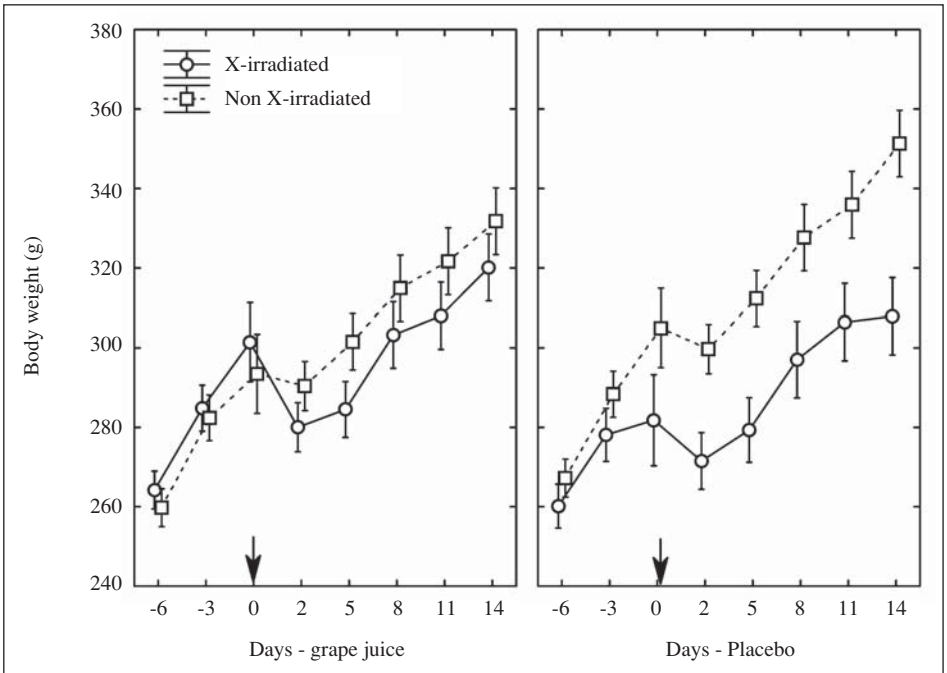
The evaluation of the body weight changes before and after X-irradiation (fig. 1) showed significant dif-

Table III
Hematological parameters obtained at 6, 24, 48 hours, and 16 days after whole-body X-irradiation of 6 Gy in male Wistar rats

Time/Group		*Erythrocyte (x 10^9/L)*	*Hemoglobin (x 10^9/L)*	*Hematocrit (x 10^9/L)*	*Platelets (x 10^9/L)*
6 h	MN	8.25 ± 0.02	17.0 ± 0.13	46.8 ± 0.4	735 ± 18
	MR	8.16 ± 0.25	17.0 ± 0.15	47.3 ± 0.6	707 ± 57
	GR	8.44 ± 0.28	17.6 ± 0.27	48.4 ± 0.5	739 ± 57
	GN	8.18 ± 0.06	17.2 ± 0.20	47.5 ± 0.7	730 ± 74
24 h	MN	8.20 ± 0.17	16.5 ± 0.39	45.0 ± 0.6	742 ± 39
	MR	7.78 ± 0.16	15.7 ± 0.27	43.5 ± 0.9	681 ± 67
	GR	7.97 ± 0.17	16.1 ± 0.42	44.3 ± 1.2	668 ± 21
	GN	7.98 ± 0.12	16.5 ± 0.29	44.8 ± 1.0	673 ± 53
48 h	MN	7.82 ± 0.10	16.0 ± 0.23	44.0 ± 0.7	739 ± 47
	MR	7.57 ± 0.12	**15.3 ± 0.24#**	42.4 ± 0.9	674 ± 75
	GR	8.02 ± 0.19	16.0 ± 0.17	44.8 ± 0.8	553 ± 63
	GN	7.89 ± 0.12	16.0 ± 0.21	43.7 ± 0.5	668 ± 32
16 d	MN	7.50 ± 0.18	15.6 ± 0.27	38.4 ± 0.7	504 ± 39
	MR	**4.69 ± 0.07***#	**9.6 ± 0.32***#	**24.6 ± 0.8***#	**66 ± 18***#
	GR	**4.25 ± 0.86***#	**8.2 ± 1.91***#	**21.3 ± 4.2***#	**80 ± 35***#
	GN	7.83 ± 0.19	16.2 ± 0.30	40.1 ± 1.0	494 ± 16

MN (grape juice only), MR (grape juice + X-irradiation), GR (placebo + X-irradiation) and GN (placebo only).
Means ± s.e.m. of 4 animals per group. Significant differences from non-irradiated groups at $p < 0.05$ (Newman-Keuls test) are indicated as *(MN) and #(GN).

ferences from the irradiated grape juice group (MR) in comparison to the placebo one, even though both presented significant body weight loss. Non-irradiated groups showed the same growth pattern for both juice and placebo ones. The irradiated grape juice group showed no significant deviation when compared to the non-irradiated one. On the other hand, a significant deviation was found in placebo group after irradiation,



Means ± s.e.m. for 4 animals in groups offered grape juice (left) or placebo (right). The arrow indicates the time of whole-body X-irradiation.

Fig. 1.—Evolution of body weight before and after X-irradiation.

Table IV
Body weight and weight of selected organs (g) 16 days after whole-body X-irradiation of 6 Gy in male Wistar rats

Group	*Body weight*	*Liver*	*Spleen*	*Kidneys*	*Heart*	*Hepatosomatic index*
MN	331.8 ± 2.6	12.2 ± 0.70	0.82 ± 0.02	2.19 ± 0.09	0.93 ± 0.01	3.68 ± 0.19
MR	320.2 ± 8.7	12.3 ± 0.83	**0.53 ± 0.03***#	2.07 ± 0.08	1.06 ± 0.04	3.83 ± 0.17
GR	**307.9 ± 9.5**#	**9.9 ± 0.46***#	**0.54 ± 0.01***#	2.01 ± 0.18	1.08 ± 0.13	**3.23 ± 0.06***#
GN	351.3 ± 11.5	12.3 ± 0.45	0.75 ± 0.03	2.29 ± 0.08	1.03 ± 0.01	3.50 ± 0.02

MN (grape juice only), MR (grape juice + X-irradiation), GR (placebo + X-irradiation) and GN (placebo only).
Significant differences from non-irradiated groups at $p < 0.05$ (Newman-Keuls test) are indicated as *(MN) and #(GN).

where a remarkable weight loss took place. The average body weight in the grape juice group was closer to the non-irradiated group than placebo, indicative that grape juice seems to protect against X-irradiation[24] over total body weight loss.

Significant differences from non-irradiated groups (table IV) were found for liver, spleen and hepatosomatic index, but not for heart and kidneys, suggestive of a higher radioresistance of these latter tissues, at least on the time window explored here. No liver weight differences were found for MR, MN and GN groups. However, GR showed considerable liver weight loss in comparison to MR and all other groups. Previous reports have shown increased liver weight 6h after X-irradiation in rats[25] and abnormalities due to small intestine X-radiation exposure, leading to changes on glycogen levels and liver function.[26,27] The present work shows that there was significant liver weight loss after 16 days for GR group, but not for MR group, which is suggestive of a radioprotective action of black grape juice supplementation. The composition of the ecologically-grown black grape juice shows a high content of bioactive phenolic compounds such as resveratrol, quercetin and rutin,[19] and it is tempting to link the radiomodifying actions of black grape juice to these chemicals. Flavonoids are known to have important antioxidant and anti-inflammatory activities.[28,29] Resveratrol has been since long studied not only as a potential antioxidant stimulating agent[30] and radiomodifier,[24,31] but also because of its anti-mutagen action, its role in mediating anti-inflammatory effects, anti-carcinogenic action by the inhibition of cyclooxygenase and hydroperoxidase activities.[32] Resveratrol has also been shown to influence the apoptotic effects of cytokines, chemotherapeutic agents, and ionizing radiation.[33] Pharmacokinetic studies of resveratrol activity revealed that its main target organs are liver and kidney,[33] where its conversion into a sulfated form and a glucuronide conjugate takes place. Nevertheless, quercetin and rutin are per se antioxidant agents[34] and so might be potentially co-responsible for the radiomodifying effect of black grape juice we are starting to see from this study.

It must also be commented out the voluntary nature of black grape juice intake by rats. There was a high individual variability, but all animals from MR and MN groups drank at least 2 ml from a maximum allowable of 10 ml. The placebo solution, on the contrary, was more palatable, with a minimum of 8 out of 10 ml being drank daily. The choice of ceiling for supplement intake was made based on previous considerations of the potential effect of black grape juice on ex vivo studies with human volunteers.[35] Food intake was severely decreased by 63±4% the first day after irradiation, but it increased thereafter, to be totally resumed 5 days post-irradiation, without differences due to grape juice supplementation (data not shown). Water intake increased by 49 ± 5% in all groups, X-irradiated and controls, on the irradiation day, but resumed to normal the next day onwards. This effect was attributed to the anesthesia procedure all animals suffered.

Conclusions

The authors studied the radiomodifier effect of organic grape juice through changes of physiological and hematological parameters in whole body X-irradiated rats. Most of the results are in agreement to the scientific background concerning to non-irradiated groups response and add new, albeit non conclusive, observations. Ecologically-grown grape juice seems to have a radiomodifier effect over selected hematological parameters on whole body X-irradiated rats. The remarkable result was the maintenance of a normal liver weight for MR group, in comparison to GR group, which had become 25% smaller. There is a background support for the idea that glucose and fructose intake is able to induce liver weight gain.[27] In spite of this liver weight gain, there are many experimental data supporting the reduction on glucose and fructose absorption by small intestine, which could imply to reduce the amount of sugar reaching to liver, leading to a consequent reduction on its conversion to fat. Non-conclusive effects were found for haematological parameters in relation to the radiomodifying effect of black grape juice intake, albeit percent granulocyte count showed significant increase at 48 hours post-irradiation in MR group. The anemia and leucopenia observed at 16 days post-irradiation are suggestive of significant damage to bone marrow tissue. More detailed experiments must be carried out in order to improve our understanding

about the radiomodifying effect of ecological grape juice over blood cells and liver function.

Acknowledgements

This work has been supported by a study-leave grant from CAPES (Brazil) and Ministerio de Educación y Ciencia (Spain) through the Brazil-Spain cooperation project PHB2007-0071-PC. Additional support from Department of Biomedical Sciences (University of León) is also acknowledged.

References

1. Maisin JR. Bacq and Alexander award lecture chemical radioprotection: past, present and future prospects. *In J Radiat Biol* 1998; 73: 443-450.
2. Hosseinimehr SJ. Fondation Review: Trends in the development of radioprotective agents. *Drug Discovery Today* 2007; 12 (19-20): 794-805.
3. Khodarev NN, Kataoka Y, Murley JS, Weichselbaum RR, Grdina DJ. Interaction Of Amifostine And Ionizing Radiation On Transcriptional Patterns Of Apoptotic Genes Expressed In Human Microvascular Endothelial Cells (HMEC). *Int J Rad Onc Biol Phys* 2004; 60 (2): 553-563.
4. Mccumber LM. The Potential Influence Of Cell Protectors For Dose Escalation In Cancer Therapy: An Nalysis Of Amifostine. *Medical Dosimetry* 2004; 29 (2): 139-143.
5. Manzi FR, Boscolo FN, Almeida SM et al. Morphological study of the radioprotective effect of vitamin E (dl-alpha-tocopheril) in tissue reparation in rats. *Radiol Bras* 2003; 36 (6): 367-371.
6. Singh VK, Srinivasan V, Toles R et al. Radiation Protection by the Antioxidant Alpha-Tocopherol Succinate, Human Factors and Medicine Panel Research Task Group 099 "*Radiation Bioeffects and Counter-measures*" meeting, held in Bethesda, Maryland, USA, 2005.
7. Khalil A, Milochevitch C. Study of the antioxidant effect of a-tocopherol on low-density lipoprotein peroxidation induced at low and high ?-radiation dose rates, *Rad Phys and Chem* 2005; 72: 347-353.
8. Ahmed RG. Damage Pattern as Function of Various Types of Radiations *Med J of Islamic World Acad of Sci* 2005; 15: 135-147.
9. Hall EJ, Giaccia AJ. Clinical Response to Normal Tissues, In: *Radiobiology for the Radiologist* 2006; chapter 19, p. 349, 6th ed.
10. Walker RI, Cerveny RJ. Medical Consequences of Nuclear Warfare. Falls Church, VA: Office of the Surgeon General, 1989.
11. Hall EJ, Giaccia AJ. Acute effects of total-body irradiation. In: Hall EJ. *Radiobiology for the Radiologist*. 2006; chapter 8, p. 349, 6th ed.
12. Waselenko JK, MacVittie TJ, Blakely WF et al. Strategic National Stockpile Radiation Working Group. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Annals of Internal Medicine* 2004; 140: 1037-51.
13. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment following severe radiation accidents. *Health Phys* 1997; 72: 513-8.
14. Baranov AE, Guskova AK, Nadejina NM, Nugis VY. Chernobyl experience: biological indicators of exposure to ionizing radiation. *Stem Cells* 1995; 13 (Supl. 1): 69-77.
15. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment in criticality accidents. *Health Phys* 2001; 81: 446-9.
16. Fliedner TM**,** Friesecke, I, Beyrer K**.** Organ specific manifestations of the acute radiation syndrome, in: *Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome***.** Oxford**:** British Institute of Radiology**;** 2001 (3): 13-38.
17. Carsten RE, Bachand AM, Bailey SM, Ullrich RL. Resveratrol reduces radiation-induced chromosome aberration frequencies in mouse bone marrow cells. *Radiat Res* 2008; 169 (6): 633-8.
18. Creager ANH, Santesmases MJS. Radiobiology in the Atomic Age: Changing Research Practices and Policies in Comparative Perspective, *Journal of the History of Biology* 2006; 39: 637-647.
19. Machado MM, Santos GFF, Rocha MIU, Andrade ER et al. Phenolic Content and Antioxidant Effect of Red Grape Juices and Wine Vinegars from Organically or Conventionally produced grapes, *Food Chemistry* 2009 (in press).
20. Hill R, Kiyasu J, Chaikoff IL. Metabolism of Glucose and Fructose in Liver of the Rat Subjected to Whole-Body X-Irradiation, *Am J Physiol* 1956; 187: 417-421.
21 Farrar JT, Small MD, Bullard D, Ingelfinger FJ. Effect of Total Body Irradiation on Absorption of Sugars From theSmall Intestine. *Am J Physiol* 1956; 186: 549-553.
22. Umegaki K, Sugisawa A, Shin SJ, Yamada K, Sano M. Different onsets of oxidative damage to DNA and lipids in bone marrow and liver in rats given total body irradiation. *Free Radic Biol Med* 2001; 31 (9): 1066-74.
23. Lee TJ, Kwon HC, Kim JS, Im SK, Choi KC. The Radiation Effect on Peripheral Blood Cell. *J Korean Soc Ther Radiol* 1988; 6 (2): 253-258.
24. Koide K, Epperly MW, Franicola D, et al. Acetylated Resveratrol: A New Small Molecule Radioprotector. *Paper presented at: Annual Meeting of American Society for Therapeutic Radiology and Oncology (ASTRO)*, 2008.
25. Supplee H, Weinman EO, Entenman C. Enlargement of the Liver in Sprague-Dawley Rats Following Whole-Body X-Irradiation. *Am J Physiol* 1956; 185: 583-588.
26. Lluch M, Ponz F. Immediate effects of x-irradiation on the intestinal absorption of glucose and radioprotection by cysteamine. *Rev Esp Fisiol* 1966; 22 (3): 109-14.
27. Ord MG, Stocken LA, Biochemical Effects of Ionizing Radiation. *Annual Review of Nuclear Science* 1959; 9: 523-552.
28. González-Gallego J, Sánchez-Campos S, Tuñón MJ. Anti-inflammatory properties of dietary flavonoids. *Nutr Hosp* 2007; 22 (3): 287-93.
29. Martínez-Flórez S, González-Gallego J, Culebras JM, Tuñón MJ. Los flavonoides: propiedades y acciones antioxidantes. *Nutr Hosp* 2002; XVII (6): 271-278.
30. Dani C, Oliboni LS, Pasquali MAB et al. Intake of Purple Grape Juice as a Hepatoprotective Agent in Wistar Rats. *J Med Food* 2008; 11 (1): 127-132.
31. Reagan-Shaw S, Mukhtar H, Ahmad N. Resveratrol Imparts Photoprotection of Normal Cells and Enhances the Efficacy of Radiation Therapy in Cancer Cells, *Photochemistry and Photobiology*. 2008; 84: 415-421.
32. Jang M, Cai L, Udeani GO, Slowing KV et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 1997; 275: 218-220.
33. Aggarwal BB, Bhardwaj A, Aggarwal RS et al. Role of Resveratrol in Prevention and therapy of Cancer: Preclinical and Clinical Studies. *Anticancer Res*. 2004; 24 (5A): 2783-840.
34. Silva J, Herrmann SM, Heuser V et al. Evaluation of the genotoxic effect of rutin and quercetin by comet assay and micronucleus test. *Food Chem Toxicol*. 2002; 40 (7): 941-7.
35. Andrade EA, Fagundes WA, Machado MM et al. Projeto Tabagismo e Nutrigenética: efeito potencial radioprotector do suco de uva orgánico (Vitis vinifera): estudo preliminar ex vivo. *23ª Jornada Académica Integrada*, UFSM, 2008.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):304-311
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Anthropometry of height, weight, arm, wrist, abdominal circumference and body mass index, for Bolivian Adolescents 12 to 18 years - Bolivian adolescent percentile values from the MESA study

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Abstract

Anthropometry is important as clinical tool for individual follow-up as well as for planning and health policy-making at population level. Recent references of Bolivian Adolescents are not available. The aim of this cross sectional study was to provide age and sex specific centile values and charts of Body Mass Index, height, weight, arm, wrist and abdominal circumference from Bolivian Adolescents. Data from the MEtabolic Syndrome in Adolescents (MESA) study was used. Thirty-two Bolivian clusters from urban and rural areas were selected randomly considering population proportions, 3445 school going adolescents, 12 to 18 y, 45% males; 55% females underwent anthropometric evaluation by trained personnel using standardized protocols for all interviews and examinations. Weight, height, wrist, arm and abdominal circumference data were collected. Body Mass Index was calculated. Smoothed age- and gender specific 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th Bolivian adolescent percentiles(BAP) and Charts(BAC) where derived using LMS regression. Percentile-based reference data for the antropometrics of for Bolivian Adolescents are presented for the first time.

(*Nutr Hosp*. 2009;24:304-311)

Key words: *Anthropometry. Body Mass Index (BMI). Growth percentiles. Waist circumference. Abdominal circumference. Height. Weight. Adolescents. Bolivia.*

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Recibido: 5-VI-2008.
Aceptado: 1-VII-2008.

REFERENCIAS ANTROPOMÉTRICAS DE LOS ADOLESCENTES BOLIVIANOS DE 12 A 18 AÑOS: ESTATURA, PESO, CIRCUNFERENCIA DEL BRAZO, MUÑECA, Y ABDOMINAL, ÍNDICE DE MASA CORPORAL. PERCENTILES DE ADOLESCENTES BOLIVIANOS (PAB) DEL ESTUDIO MESA

Resumen

La antropometría es una herramienta clínica importante para el seguimiento individual de los pacientes así como para la planificación de políticas públicas. En Bolivia no existen referencias antropométricas nacionales para adolescentes. El objetivo de este estudio transversal fue de desarrollar percentiles y diagramas de crecimiento para peso, talla, índice de masa corporal, presión arterial sistólica y diastólica, circunferencia de muñeca, brazo y abdominal de adolescentes bolivianos. Los datos antropométricos en el estudio MESA (Síndrome metabólico en adolescentes bolivianos) fueron obtenidos a partir de 32 unidades muestrales, considerando proporcionalidad muestral con reposición. Fueron evaluados 3445 adolescentes de 12 a 18, 45% hombres; 55% mujeres, de colegios de áreas urbanas y rurales. La evaluación fue efectuada por personal entrenado siguiendo procedimientos estandarizados. Se tomaron medidas del peso, talla circunferencias de muñeca, brazo y abdominal. El índice de masa corporal fue calculado. Se obtuvieron los valores de los percentiles 3º, 5º, 10º, 25º, 50º, 75º, 85º, 90º, 95º y 97º utilizando regresión por el método LMS. Las referencias antropométricas para los adolescentes bolivianos son presentadas por vez primera a la comunidad médica. (En la versión electronica de Nutrición Hospitalaria se puede consultar el texto integro en castellano de este articulo).

(*Nutr Hosp*. 2009;24:304-311)

Palabras clave: *Antropometría. Índice de Masa Corporal (IMC). Percentiles de crecimiento. Circunferencia de la cintura. Circunferencia abdominal. Talla. Peso. Adolescentes. Bolivia.*

Introduction

Anthropometric parameters and their derived indices are frequently used by physicians and health workers as a valuable instrument to determine health and disease, to define nutritional status, to assess growth and development, to determine differences in body proportion between populations as well as to optimize diagnosis and treatment.[1-3]

Decisions for policy making and planning in public health nutrition must be based on anthropometric accurate information about the population for which it is intended to be used. Since little is known regarding anthropometry of Bolivian adolescents,[4] and no national reference percentiles or charts have been developed, international references[5-7] have been used systematically for growth monitoring and nutritional classification of individuals.

Previous studies in La Paz, and from other regions of Bolivia[4,8-10] confirmed the need for updated information to address the nutritional status of adolescents in Bolivia. The country faces nutritional transition and adolescents are among the most vulnerable group to its impact. Increased numbers of overweight and obese adolescents has been described recently.[4] For the Bolivian health system, having access to local growth references and clinical evaluation parameters for adolescents is urgent and crucial to measure trends in nutritional status and to develop concurrent policies.

Local anthropometric references are indispensable to perform high-quality clinical practices. Health care providers base their diagnosis on percentile values to decide extent of a problem and level of treatment. This is particularly true for predicting and assessing risk for cardiovascular diseases and metabolic syndrome, which uses among other factors, percentile values of Body Mass Index (BMI), abdominal circumference and blood pressure. For the assessment of high blood pressure percentiles of height is required for adolescents. The use of heights derived from other populations could induce to diagnosis error.

For nutritional intervention programs local population percentile values could help to portrait future risk associated to nutritional transition outcomes, and initiate activities to reduce morbidity and mortality rates associated with risk factors for chronic diseases, such as hyperlipidaemia, hyperinsulinaemia, hypertension, and early atheroesclerosis in adulthood.[6,11-14] Treatment of diet related diseases depletes the Bolivian limited health budget resources. Therefore interventions based in early detection and correct targeting of populations at risk is likely to reduce future expenditures.

In 2005 a national study called the MEtabolic Syndrome in Adolescents (MESA) was carried out to assess the cardiovascular and metabolic syndrome of Bolivian adolescents in relation to obesity, diabetes, income, food intake and physical activity in Bolivia. The first component of the MESA study was to document references of anthropometric parameters needed to measure risk. This document provide age and sex specific percentile values and charts of BMI, height, weight, arm, and wrist and waist circumference from Bolivian adolescents.

Methods

Sample size was estimated using Epi info v 3 Software assuming a prevalence of 2.5% obesity, at 95% confidence level. A total of 32 clusters proportional to population size, with replacement from the national list of Counties were selected randomly. A cluster was defined as a school. Schools were chosen from the corresponding Education District's list of the County. Individuals were chosen from the school register. The sample size calculated for each school was 120 subjects, about 20 per grade from 7th to 12th grade. Data was collected from September 2005 to June 2007.

The random selection ensured that the Bolivian population from the Andean highlands, valleys and tropics were appropriately represented. Rural, semi-urban and urban settings were also represented in the sample. The study protocol was approved by the ethics committee of the Universidad del Valle and the Bolivian Ministry of Education. Ethical procedures comply with the Helsinki declaration of 1975 reviewed in 2000.[15] Informed consent was obtained from all participants, and a parent or legal guardian.

Adolescents completed a self administered questionnaire on sociodemographic, nutritional intake and physical activity aspects. A date for a school visit was scheduled for data collection.

Weight, height, wrist, arm and abdominal circumference were recorded twice for each individual by trained personnel following WHO's recommendations.[1] Average values were used for the analysis. Weight was recorded in light, indoor clothing with a Beurer's digital scale to the nearest 0.1 kg, height was measured without shoes to the nearest 0.1 cm using a portable metal stadiometer. Abdominal circumference was measured to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration when the participant was in a standing position, using a steel measuring tape following WHO recommendations.[1] Pregnant adolescents were excluded.

For each participant of all locations, the same equipment was used for the anthropometric measurements. All evaluations were carried out from eight to eleven in the morning. Data quality was assured by previous extensive training of the medical assistants.

BMI was calculated applying the standard formula: Weight in kilograms divided by the square of height.

For comparability with other studies, the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentiles were chosen as reference values. Smoothed age- and gender specific values and charts for each percentile value and for each anthropometric index where derived using the least median squares (LMS) regression. The Cole's

Table I
Anthropometric characteristics of the sample by age: Mean (SD)

		Boys				Girls			
Age	*n = 3,445*	*n*	*Weight (kg)*	*Height (cm)*	*BMI (kg/m²)*	*n*	*Weight (kg)*	*Height (cm)*	*BMI (kg/m²)*
12	342	172	43.8 (9.93)	147.6 (8.7)	19.9 (3.4)	170	44.4 (9.4)	149.1 (7.4)	19.8 (3.2)
13	435	221	47.4 (9.98)	153.7 (8.2)	19.9 (3.2)	214	47.6 (7.8)	152.1 (7.9)	20.6 (3.1)
14	486	221	52.6 (10.0)	160.9 (8.0)	20.3 (2.9)	265	51 (8.4)	153.3 (5.7)	21.7 (3.3)
15	621	267	55.0 (10.0)	163.0 (6.7)	20.7 (3.0)	354	52.7 (7.3)	154.7 (5.8)	22.0 (2.9)
16	717	306	57.5 (7.9)	165.2 (6.7)	21 (2.4)	411	54.0 (8.2)	154.3 (6.2)	22.6 (3.0)
17	561	220	58.6 (2.8)	165.5 (6.8)	21.4 (2.8)	341	54.5 (8.7)	154.9 (6.1)	22.7 (3.4)
18	283	144	60.3 (8.5)	166.6 (6.0)	21.7 (2.7)	139	56.8 (9.4)	155.4 (6.5)	23.4 (3.4)

LMS method[16] also called maximum penalized likelihood approach was used because it has proven to be a powerful and compact technique for deriving and presenting reference charts. It calculates the Box-Cox power needed to transform the data to normality at each age, and displaying the results as a smooth curve of power plotted against age allowing the original centiles to be reconstructed to high accuracy. The LMS Pro software used for data management was obtained from the institute of Child Health, London. Descriptive statistics were computed using SPSS v 12 and graphs and charts from LMSChartMaker 2006.

Results

Data was collected on 3,445 adolescents, 1,551 boys and 1,894 girls, from rural (34.8%) and urban areas (65.2%), and from public (76.4%) and private (23.6%) schools. Although 4,013 adolescents were selected initially to participate on the study, 3,445 finally participated in the study. Adolescents dropped out of the study due to refusal of parental consent, failure to attend the day of data collection, failure to fill the birth date or name, failure to return the questionnaire or failure to have their anthropometric data taken or completed. Characteristics of the population sample by age are presented in table I.

Table II to VII shows smoothed percentile values respectively for BMI, height, weight, abdominal, arm and wrist circumference by age- and gender.

Figures 1 to 12 show the smoothed charts for each anthropometric parameter in order to be available for practical clinical application.

Conclusion

Smoothed age- and gender specific 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th Bolivian adolescent per-

Table II
Body Mass Index (BMI) percentile values for Bolivian adolescents 12th to 18th years, by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	14.9	15.3	16.1	17.5	19.3	21.5	22.8	23.8	25.4	26.5
13	15.9	16.4	17.1	18.5	20.3	22.4	23.8	24.7	26.3	27.5
14	16.9	17.3	18.0	19.4	21.1	23.2	24.5	25.5	27.1	28.3
15	17.6	18.0	18.7	20.0	21.7	23.8	25.1	26.1	27.7	28.9
16	18.0	18.4	19.1	20.4	22.1	24.2	25.5	26.5	28.2	29.4
17	18.3	18.7	19.4	20.6	22.4	24.5	25.9	27.0	28.8	30.1
18	18.5	18.9	19.6	20.9	22.7	24.9	26.4	27.5	29.4	30.9
Boys										
12	15.1	15.4	16.1	17.3	19.1	21.3	22.7	23.9	25.9	27.5
13	15.6	16.0	16.6	17.8	19.5	21.6	22.9	24.0	25.8	27.1
14	16.1	16.5	17.1	18.3	19.9	21.8	23.1	24.0	25.7	26.9
15	16.7	17.0	17.6	18.8	20.3	22.1	23.3	24.2	25.6	26.7
16	17.1	17.5	18.1	19.2	20.7	22.5	23.6	24.4	25.8	26.8
17	17.5	17.8	18.4	19.6	21.0	22.8	23.9	24.7	26.1	27.0
18	17.7	18.1	18.7	19.8	21.3	23.1	24.2	25.1	26.4	27.4

Table III
Height percentile values (m) for Bolivian adolescents 12th to 18th years by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	1.35	1.37	1.40	1.44	1.49	1.54	1.56	1.58	1.61	1.63
13	1.40	1.41	1.43	1.47	1.52	1.56	1.59	1.60	1.63	1.65
14	1.42	1.44	1.46	1.49	1.53	1.58	1.60	1.61	1.64	1.65
15	1.43	1.45	1.47	1.50	1.54	1.58	1.61	1.62	1.64	1.66
16	1.44	1.45	1.47	1.51	1.55	1.59	1.61	1.62	1.65	1.66
17	1.44	1.45	1.47	1.51	1.55	1.59	1.61	1.63	1.65	1.67
18	1.44	1.45	1.47	1.51	1.55	1.60	1.62	1.63	1.66	1.67
Boys										
12	1.33	1.35	1.38	1.43	1.48	1.54	1.57	1.59	1.59	1.65
13	1.40	1.41	1.44	1.49	1.55	1.60	1.63	1.65	1.65	1.70
14	1.45	1.47	1.50	1.55	1.60	1.65	1.68	1.70	1.70	1.75
15	1.50	1.51	1.54	1.58	1.63	1.68	1.71	1.72	1.72	1.77
16	1.52	1.54	1.56	1.60	1.65	1.69	1.72	1.74	1.74	1.78
17	1.54	1.55	1.58	1.62	1.66	1.70	1.73	1.74	1.74	1.78
18	1.55	1.57	1.59	1.63	1.67	1.71	1.73	1.74	1.74	1.78

Table IV
Weight percentile values (kg) for Bolivian adolescents 12th to 18th years by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	30.8	32.0	34.0	37.8	42.7	48.6	52.2	54.9	59.3	62.4
13	35.2	36.4	38.3	42.0	46.8	52.5	56.1	58.7	63.1	66.1
14	38.6	39.7	41.6	45.1	49.7	55.3	58.8	61.4	65.6	68.6
15	40.9	42.0	43.8	47.2	51.7	57.1	60.5	63.1	67.2	70.3
16	42.1	43.2	45.0	48.3	52.8	58.2	61.7	64.3	68.6	71.7
17	42.8	43.9	45.7	49.0	53.5	59.1	62.7	65.5	70.1	73.5
18	43.4	44.4	46.2	49.6	54.2	60.0	63.9	66.8	71.8	75.6
Boys										
12	28.7	30.0	32.3	36.6	42.2	49.1	53.3	56.5	61.6	65.3
13	33.2	34.6	36.8	41.1	46.7	53.6	57.9	61.2	66.5	70.3
14	37.6	38.9	41.1	45.3	50.8	57.5	61.7	64.9	70.2	74.0
15	41.4	42.6	44.7	48.6	53.8	60.2	64.2	67.2	72.1	75.8
16	44.4	45.6	47.6	51.3	56.1	62.0	65.7	68.5	73.1	76.4
17	46.6	47.7	49.6	53.1	57.7	63.3	66.8	69.4	73.7	76.9
18	48.4	49.5	51.3	54.6	59.0	64.3	67.6	70.1	74.2	77.3

centiles(BAP) and Charts(BAC) for the anthropometric parameters of height, weight, arm, wrist, and abdominal circumference and body mass index for Bolivian Adolescents 12 to 18y were developed.

The data of the sample distribution resembles the population distribution of the country. As stated in the 2007 projection of the 2001 National Census[17;18] the urban and rural population is estimated respectively at 65.4% and 34.6%. The study was carried out with school attending adolescents missing the ones that do not attend it, thus no claim can be made for complete representativeness. However there is no indication that anthropometric values of this group could vary due to genetic factors from the adolescents that have participated in the study. This factor may on the other hand have reduced data collection from a more vulnerable adolescent population that may have suffered more from infection or disease two elements that can negatively affect malnutrition and growth.

Anthropometry provides the single most convenient, universally applicable, inexpensive and non-invasive technique for assessing size, proportions and composition of the human body. It reflects both health and nutritional status and predicts performance, health and survival.[1,4]

Table V
Abdominal circumference percentile values (cm) for Bolivian adolescents 12th to 18th years by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	57.7	58.8	60.6	64.0	68.3	73.5	76.7	79.1	83.0	85.9
13	60.0	61.1	62.9	66.3	70.7	75.8	79.1	81.4	85.3	88.1
14	61.7	62.9	64.7	68.1	72.5	77.8	81.0	83.4	87.3	90.1
15	63.0	64.1	66.0	69.4	73.9	79.2	82.4	84.9	88.8	91.7
16	63.7	64.9	66.7	70.3	74.8	80.2	83.5	86.0	90.1	93.0
17	64.0	65.2	67.1	70.7	75.4	81.0	84.5	87.0	91.3	94.4
18	64.3	65.5	67.5	71.2	76.0	81.8	85.4	88.1	92.6	95.9
Boys										
12	57.7	58.8	60.6	64.0	68.7	74.7	78.6	81.7	87.0	91.1
13	60.5	61.5	63.2	66.4	70.7	76.2	79.9	82.7	87.7	91.5
14	63.1	64.0	65.6	68.5	72.5	77.6	80.9	83.5	88.1	91.6
15	65.2	66.1	67.5	70.3	74.0	78.6	81.7	84.1	88.2	91.3
16	66.7	67.5	68.9	71.5	75.0	79.4	82.2	84.5	88.3	91.3
17	67.5	68.3	69.7	72.2	75.6	79.8	82.6	84.8	88.6	91.6
18	68.2	69.0	70.3	72.7	76.1	80.3	83.1	85.3	89.1	92.1

Table VI
Arm circumference percentile values (cm) for Bolivian adolescents 12th to 18th years by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	18.2	18.6	19.3	20.6	22.2	24.1	25.3	26.1	27.5	28.4
13	19.1	19.5	20.2	21.4	23.0	24.8	26.0	26.8	28.2	29.1
14	19.9	20.3	20.9	22.1	23.6	25.4	26.5	27.4	28.7	29.7
15	20.4	20.8	21.4	22.6	24.0	25.8	26.9	27.7	29.0	30.0
16	20.7	21.1	21.7	22.8	24.3	26.0	27.1	28.0	29.3	30.3
17	20.9	21.3	21.9	23.0	24.4	26.2	27.4	28.2	29.7	30.8
18	21.1	21.5	22.1	23.2	24.7	26.5	27.7	28.6	30.1	31.3
Boys										
12	17.9	18.3	19.0	20.2	21.8	23.8	25.0	26.0	27.5	28.6
13	18.7	19.2	19.8	21.1	22.7	24.6	25.7	26.6	28.0	28.9
14	19.5	19.9	20.6	21.8	23.4	25.2	26.3	27.1	28.3	29.2
15	20.1	20.5	21.2	22.4	24.0	25.7	26.7	27.4	28.6	29.4
16	20.7	21.1	21.8	23.0	24.5	26.2	27.2	27.9	29.0	29.7
17	21.1	21.5	22.2	23.5	25.1	26.7	27.7	28.4	29.5	30.2
18	21.5	22.0	22.7	24.0	25.6	27.3	28.3	29.0	30.1	30.8

For adolescents it is also useful to determine biological maturity and health risks. To the knowledge of the authors, this is the largest anthropometric survey carried out in Bolivia, providing nationally representative data. Bolivian health providers have for the first time locally developed anthropometric tables and charts at their disposal, to assess the nutritional status of Bolivian adolescents 12 to 18 y which can also to be used for other clinical applications.

Several characteristics make this tool valuable and reliable: they came from a large set of data, in which all the 327 Counties of Bolivia had similar opportunity to be selected, rural and urban areas were represented at the same level of distribution as the general population, all ages and gender of adolescents from 12 to 18th year were assessed in the same study, following a standard protocol, using the same equipment and carried out by the same research team.

It is important to mention that percentile values and charts came from a descriptive study that portraits the present situation of adolescents, and does not claim to be a standard that describes a population that followed healthy recommendations for all parameters that could affect normal growth and body composition, or a population that have developed its full genetic potential. Values and charts must be used for this reason with

Table VII
Wrist percentile values (cm) for Bolivian adolescents 12th to 18th years by age and gender

Percentile	*3th*	*5th*	*10th*	*25th*	*50th*	*75th*	*85th*	*90th*	*95th*	*97th*
Age										
Girls										
12	13.0	13.3	13.6	14.3	15.0	15.8	16.2	16.5	17.0	17.3
13	13.4	13.6	14.0	14.6	15.3	16.0	16.4	16.7	17.1	17.4
14	13.7	13.9	14.2	14.8	15.5	16.2	16.6	16.8	17.3	17.5
15	13.9	14.1	14.4	14.9	15.6	16.2	16.6	16.9	17.3	17.6
16	13.9	14.1	14.4	14.9	15.6	16.3	16.7	17.0	17.4	17.7
17	13.9	14.1	14.4	14.9	15.6	16.3	16.8	17.1	17.5	17.8
18	13.8	14.1	14.4	15.0	15.7	16.4	16.9	17.2	17.7	18.1
Boys										
12	13.1	13.4	13.8	14.4	15.2	16.1	16.6	17.0	17.5	17.9
13	13.6	13.9	14.2	14.9	15.7	16.5	17.0	17.3	17.8	18.1
14	14.0	14.3	14.7	15.3	16.0	16.8	17.2	17.5	18.0	18.3
15	14.3	14.6	14.9	15.5	16.2	16.9	17.3	17.6	18.0	18.3
16	14.6	14.8	15.1	15.7	16.4	17.1	17.4	17.7	18.1	18.3
17	14.7	14.9	15.3	15.9	16.5	17.2	17.6	17.8	18.2	18.4
18	14.8	15.0	15.4	16.0	16.7	17.3	17.7	17.9	18.3	18.5

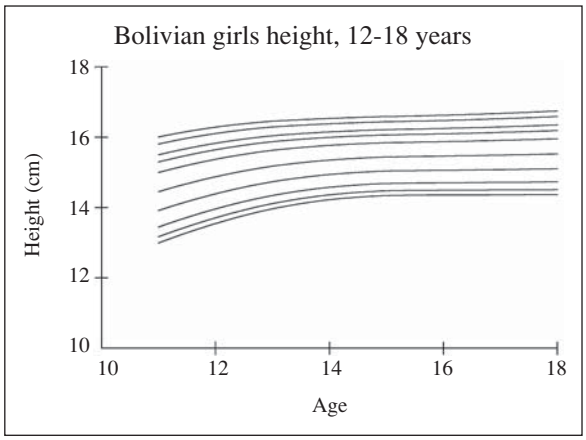

Fig. 1.—Height curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

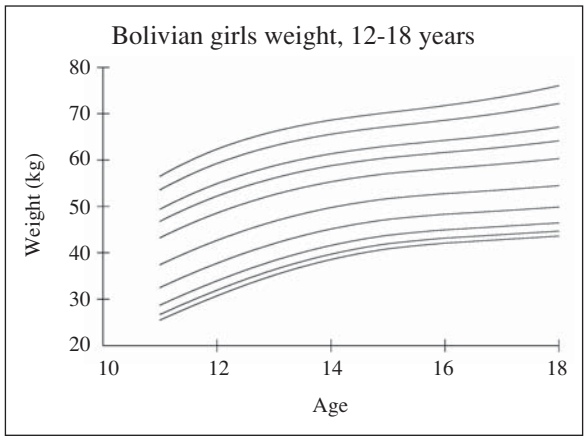

Fig. 3.—Weight curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

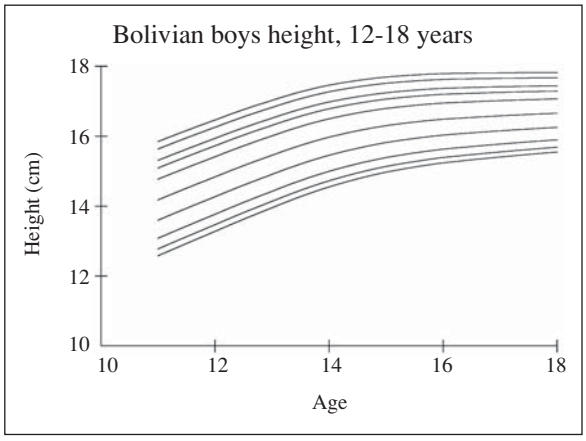

Fig. 2.—Height curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian boys 12th-18th years.

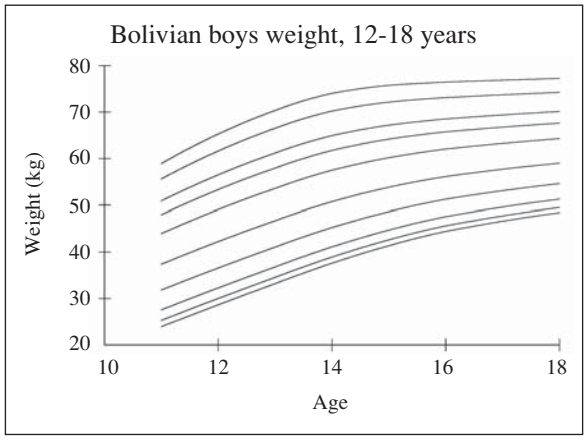

Fig. 4.—Weight curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian boys 12th-18th years.

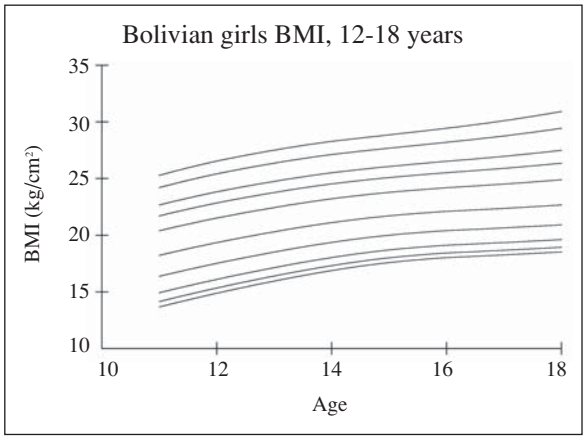

Fig. 5.—Body Mass Index (BMI) curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

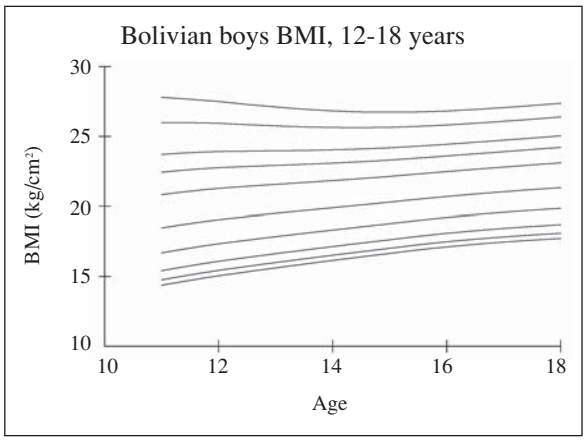

Fig. 6.—Body Mass Index (BMI) curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian boys 12th-18th years.

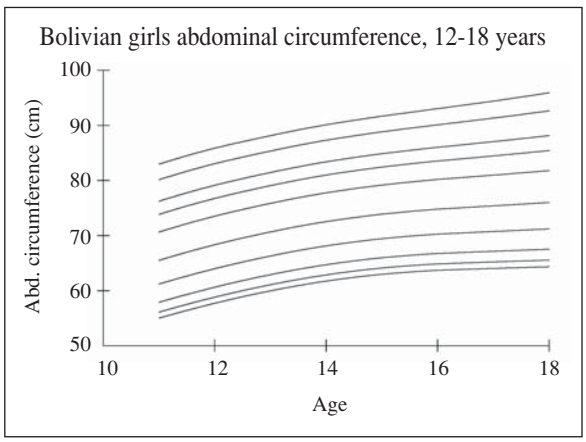

Fig. 7.—Abdominal circumference curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

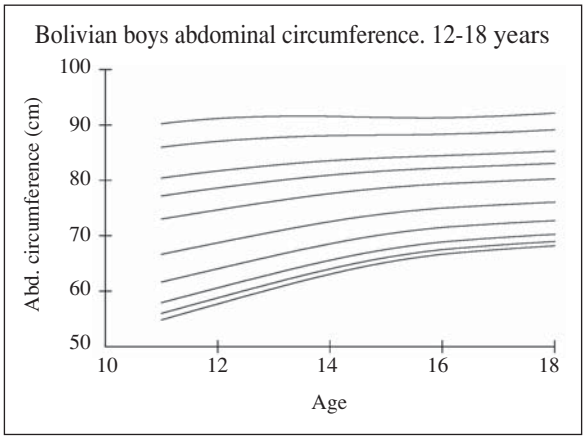

Fig. 8.—Abdominal circumference curves for the 3rd. 5th. 10th. 25th. 50th. 75th. 85th, 90th. 95th and 97th percentile of Bolivian girls 12th-18th years.

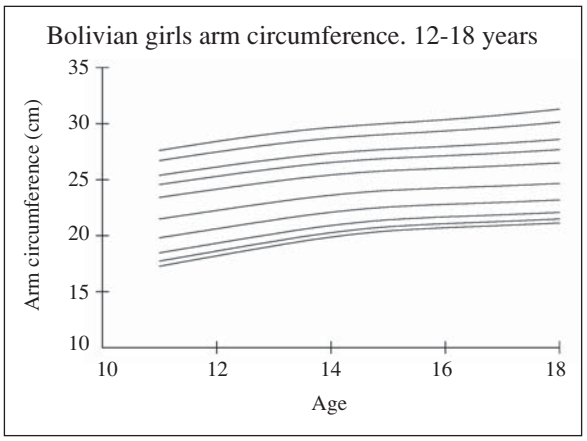

Fig. 9.—Arm circumference curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

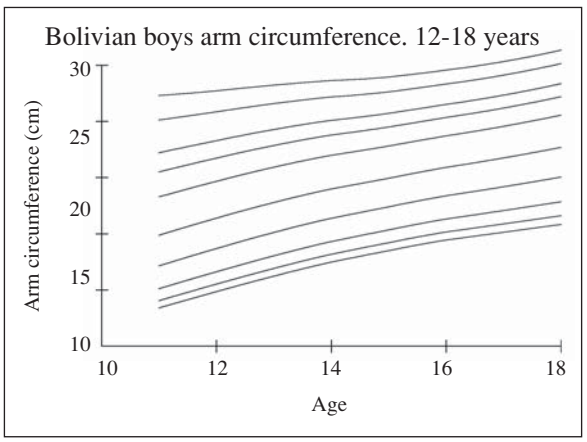

Fig. 10.—Arm circumference curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian boys 12th-18th years.

caution by the medical community. Once an international or a national reference that considers these aspects is developed, the BAP must be replaced by it.

Clearly there will be quantitative and qualitative dimensions to consider with the introduction of the newly developed Bolivian Adolescent Percentiles

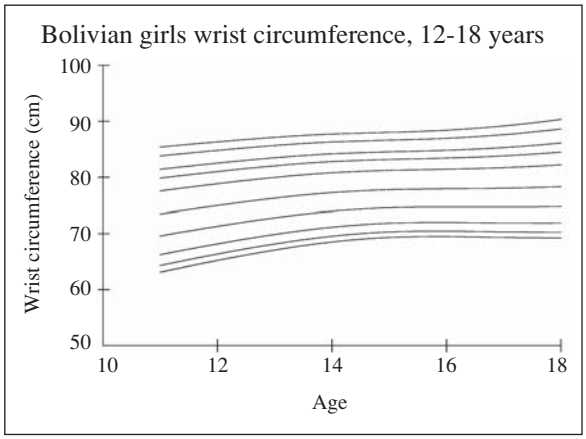

Fig. 11.—Wrist circumference curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian girls 12th-18th years.

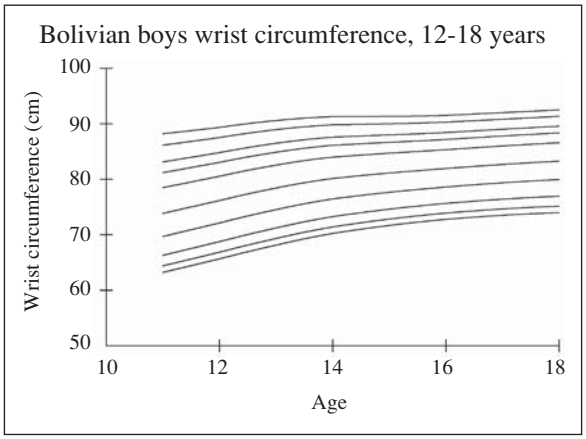

Fig. 12.—Wrist circumference curves for the 3rd, 5th, 10th, 25th, 50th, 75th, 85th, 90th, 95th and 97th percentile of Bolivian boys 12th-18th years.

(BAP) Reference in replacement of the CDC or other international available references such as the IOTF. There is a need to compare the performance of these different References in their ability to classify individuals according to their nutritional status or to diagnose the risk of chronic disease in this population.

It may be that the criteria to identify adolescents at risk of overweight or a biochemical imbalance needs to be revised when differences are observed in sensitivity and specificity between the different references for a variety of outcome parameters.

Acknowledgments

The authors wish to thank the adolescents, their parents, and school directors from the 32 locations were the studies were conducted. Also to students and the staff of the Faculty of Medicine of the Universidad del Valle as well as the personnel of other institutions for their cooperation during different steps of the study. Special thanks go to the Prince Leopold Institute of Tropical Medicine who has supported this study and to Nutrition Third World for making it possible through funding it.

References

1. WHO. Physical status : The use and interpretation of anthropometry. Report of a WHO Expert Committee. 1995; 854: 1-453. Geneva, WHO. WHO Technical Report Series. Ref Type: Report.
2. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988; 41: 105-14.
3. De Onis M, Garza C, Onyango AW, Martorell R. WHO Child growth standards. Taylor and Francis, 2006.
4. Pérez-Cueto A, Almanza M, Kolsteren P. Female gender and wealth are associated to overweight among adolescents in La Paz, Bolivia. *Eur J Clin Nutr* 2005; 59: 82-7.
5. Ogden CL, Kuczmarski RJ, Flegal KM et al. Centers by Disease Control and Prevention 200 growth charts for the United States: Improvements to the 1977 National Center for Health Statistical version. *Pediatrics* 2002; 109: 45-60.
6. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320: 1240-3.
7. Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007; 8: 299-306.
8. Pérez-Cueto FJA, Naska A, Monterrey J, Almanza-López M, Trichopoulou A, Kolsteren P. Monitoring food and nutrient availability in a nationally representative sample of Bolivian households. *BJN* 2006; 95: 555-567.
9. Pérez-Cueto FJ, Kolsteren P. Changes in the nutritional status of Bolivian women 1994-1998: demographic and social predictors. *Eur J Clin Nutr* 2004; 58: 660-6.
10. Benefice E, López R, Monroy SL, Rodríguez S. Fatness and overweight in women and children from riverine Amerindian communities of the Beni River (Bolivian Amazon). *Am J Hum Biol* 2007; 19: 61-73.
11. Zimmet P, Alberti KG, Kaufman F et al. The metabolic syndrome in children and adolescents-and IDF consensus report. *Pediatr Diabetes* 2007; 8: 299-306.
12. De Onis M, Onyango AW, Borghi E, Garza C, Yang H. Comparison of the World Health Organization (WHO) Child Growth Standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programmes. *Public Health Nutr* 2006; 9: 942-7.
13. Goran MI, Ball GD, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab* 2003; 88: 1417-27.
14. Hauner H. Insulin resistance and the metabolic syndrome-a challenge of the new millennium. *Eur J Clin Nutr* 2002; 56 (Supl. 1): S25-S29.
15. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2000; 284: 3043-5.
16. Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr* 1990; 44: 45-60.
17. Instituto Nacional de Estadistica. Bolivia Indicadores Sociodemograficos por provincial y secciones de provincial 1992-2001. Instituto Nacional de Estadistica, 2006.
18. Instituto Nacional de Estadistica. Bolivia Proyecciones de poblacion por provincias y municipios, segun sexo y grupos de edad, periodo 2000-2010. 2005.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):312-317
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Serum concentrations of vitamin A and oxidative stress in critically ill patients with sepsis

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Abstract

Introduction: **Sepsis is one of the main causes of mortality in patients in Intensive Care Units. As a result of the systemic inflammatory response and of the decrease of the aerobic metabolism in sepsis, the oxidative stress occurs. Vitamin A is recognized by the favorable effect that it exerts on the immune response to infections and antioxidant action.**

Objetive: **To bring new elements for reviewing of the nutritional support addressed to critically ill patients with sepsis, with emphasis to vitamin A.**

Methods: **Critically ill patients with sepsis had circulating concentrations of retinol, β-carotene, thiobarbituric acid-reactive substances (TBARS) and C-reactive protein (CRP) measured in Medicosurgical Intensive Care Unit in the city of Rio de Janeiro, Brazil. The patients were divided into two groups: patients who were receiving nutritional support and those without support. At the act of the patient's admission, APACHE II score was calculated.**

Results: **46 patients were studied (with diet n = 24 and without diet n = 22). Reduced levels of retinol and β-carotene were found in 65.2% and 73.9% of the patients, respectively. Among the patients who presented lower concentrations of CRP it was found higher β-carotene inadequacy (64.8%) and 50% of retinol inadequacy. There was no significant difference as regards retinol, TBARS and APACHE II levels among the patients with and without nutritional support. However, higher levels of CRP (p = 0.001) and lower levels of serum β-carotene (p = 0.047) were found in patients without nutritional support.**

Conclusions: **Septic patients presented an important inadequacy of retinol and β-carotene. The present study bring elements to the elaboration/review of the nutritional protocol directed to the group studied, especially as regards vitamin A intake.**

(*Nutr Hosp*. 2009;24:312-317)

Key words: *Sepsis. Retinol. β-carotene. Vitamin A. Oxidative stress. Critical care. C-reactive protein.*

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Recibido: 24-IX-2008.
Aceptado: 3-II-2009.

CONCENTRACIONES SÉRICAS DE VITAMINA A Y ESTRÉS OXIDATIVO EN PACIENTES CRÍTICOS CON SEPSIS

Resumen

Introducción: **La sepsis es una de las principales causas de mortalidad en pacientes en las Unidades de Cuidados Intensivos. Como consecuencia de la respuesta inflamatoria sistémica y de la disminución del metabolismo aeróbico en la sepsis se produce estrés oxidativo. La vitamina A es reconocida por el efecto favorable que ejerce sobre la respuesta inmunitaria a las infecciones y por su acción antioxidante.**

Objetivo: **Aportar nuevos elementos a la hora de revisar el soporte nutricional de los pacientes críticos con sepsis, con un énfasis sobre la vitamina A.**

Métodos: **Se midieron las concentraciones circulantes de retinol, β-caroteno, ácido tiobarbitúrico-sustancias reactivas (ATBSR) y proteína C reactiva (PCR) de pacientes críticos con sepsis en la Unidad de Cuidados Intensivos Medicoquirúrgica de la ciudad de Río de Janeiro, Brasil. Se dividió a los pacientes en dos grupos: pacientes que recibían soporte nutricional y aquellos que no. Se calculó la puntuación APACHE en el momento de su ingreso.**

Resultados: **Se estudiaron 46 pacientes (con dieta n = 24 y sin dieta n = 22). Se hallaron concentraciones disminuidas de retinol y β-caroteno en el 65,2% y 73,9% de los pacientes, respectivamente. De entre los pacientes que presentaron las menores concentraciones de PCR, se halló una mayor inadecuación de β-caroteno (64,8%) y un 50% de inadecuación de retinol. No hubo diferencias significativas con respecto al retinol, ATBSR y las puntuaciones APACHE II entre los pacientes con y sin soporte nutricional. Sin embargo, se hallaron mayores concentraciones de PCR (p = 0,001) y menores concentraciones séricas de β-caroteno (p = 0,047) en los pacientes sin soporte nutricional.**

Conclusiones: **Los pacientes sépticos presentaron una inadecuación importante de retinol y β-caroteno. El presente estudio aporta elementos a la elaboración/revisión del protocolo nutricional dirigido al grupo estudiado, especialmente con respecto de la toma de vitamina A.**

(*Nutr Hosp*. 2009;24:312-317)

Palabras clave: *Sepsis. Retinol. β-caroteno. Vitamina A. Estrés oxidativo. Atención crítica. Proteína C reactiva.*

Introduction

The survival of critical patients depends on a complex and careful immune response through all organic systems. Generally, the immune response dysfunction is present in two different ways: excessive performance of the cellular immune response that is clinically manifested as Systemic Inflammatory Response Syndrome (SIRS) and reduction of the immune response, leading to a significant increase in susceptibility to infections that result in sepsis.[1]

Sepsis, which may be considered as SIRS face to an infectious stimulus, is one of the main causes of mortality in patients in Intensive Care Units (ICUs), despite improvements in supportive and antimicrobial therapies.[2] It is characterized by multiple manifestations which can determine dysfunction or failure of one or more organs, or even death.[3] Mortality rate for severe sepsis varies between 30-50% in critical patients,[1] and it is the cause of around 2% of hospital admissions.[4] Mean sepsis incidence is 50-95 cases for every 100,000 patients and has been rising around 9% every year.[4]

As a result of systemic inflammatory response and decrease in aerobic metabolism in sepsis, oxidative stress occurs in extracellular and in intracellular spaces.[5] Oxidative stress has been implicated in human diseases by a growing body of scientific evidences,[6] and it may be defined as the situation where an increase of the physiological levels of the reactive oxygen species (ROS) occurs, resulting either from the decrease of antioxidant defense levels or from high production of ROS.[7] Oxidative stress is capable of causing lipid peroxidation of cellular membranes. Lipid peroxidation is a complex process, whereby polyunsaturated fatty acids of cellular membranes undergo reaction with oxygen to yield lipid hydroperoxides. The generation of products of lipid peroxidation after oxidative stress may be measured in the form of TBARS (thiobarbituric acid-reactive substances), where malondialdhyde stands out.[8]

Acute severe pathological conditions such as sepsis are associated with the increase of ROS production and other species of radicals with a consequent oxidative stress that will be able to exacerbate organic injury.[1]

Alterations in concentrations of some plasmatic proteins occur in critical patients such as C-reactive protein (CRP) increased production by the liver. CRP is one of the main proteins of the acute phase that has been utilized as a precocious and sensitive biomarker of the response to infectious or inflammatory processes, and it may increase from 19 to 100 times in the first 12 hours after aggression.[9]

The potential toxicity of ROS may becounteracted by antioxidants.[10,11] Antioxidants may be defined as any substance that when present in low concentrations, compared to those of oxidable substrates, significantly postpones or inhibits the oxidation of these substrates.[12]

Antioxidant systems include glutathione, vitamins (A, C and E) and several enzymes.[13] Previous studies have demonstrated that, in sepsis, an increase in the levels of oxidative stress and a decrease in the circulating concentration of antioxidant components of the defense system occur, including vitamins C, E, A and beta-carotene.[2] Antioxidant concentrations seem to increase the quantity of the immune system cells when compared to other cells.[14] Vitamin A stands out, since the favorable effect it exerts on immune response to infections is recognized.

Vitamin A participates in several primordial functions in human systems playing a role in visual acuity, cellular proliferation and differentiation, antioxidant action and immunological activity. The term vitamin A embodies the terminologies retinol and carotenoids, which are, respectively, the pre-formed vitamin and its precursors. Among these, β-carotene is recognized as the most potent retinol precursor.[15] As much its biologically active form, as its provitamin forms, have gained prominence for their role against ROS, protecting the organism against oxidative stress and, consequently, preventing damages and tissue lesions.[16] Retinol possesses antioxidant activity as it associates with peroxil radicals before these are able to propagate peroxidation to the cellular lipid component and to generate hydroperoxides. As regards carotenoids, they neutralize peroxil radicals and singlet oxygen.[17] β-carotene has an antioxidant activity five times higher than retinol.[15]

In view of this context, the present study aimed to assess the serum concentrations of retinol, β-carotene and oxidative stress and their relationship to CRP in septic patients hospitalized in ICU as a means of bringing new elements to the review of the nutritional support addressed to this group, with emphasis on the intake of vitamin A.

Materials and methods

The present study was conducted in Medicosurgical Intensive Care Unit in the city of Rio de Janeiro, Brazil. The study was approved by the Research Ethics Committee of Hospital Universitário Clementino Fraga Filho/ Universidade Federal do Rio de Janeiro (under the n.174/05). Informed consent was obtained from the patients' relatives.

All the adult patients hospitalized with sepsis diagnosis according to the International Sepsis Definitions Conference[18] were included in the study from January through December 2006. Patients who had chronic renal insufficiency, liver cirrhosis, and pregnant women, as well patients in immediate postoperative period and with parenteral nutritional support, were excluded.

At the time of enrollment in the study, patients were divided into two groups at random: patients who were receiving enteral nutritional support and those without support. According to hospital routine, the patients with nutritional support received hypercaloric enteral diet (1.5 kcal/ml) and hyperproteic diet (18 ± 2% of protein/day), and medical supplement (containing 5,000 IU/day of vitamin A).

At the act of the patient's admission, APACHE II score was calculated[19] and the following biochemical assessments were conducted:

- *Vitamin A:* Plasma retinol and β-carotene were determined by high performance liquid chromatography (HPLC).[20] Levels of serum retinol were presented by interval classes of 0.35 μmol/L (or 10 μg/dl) to allow its classification according to the recommendations of the World Health Organization.[21] This enables to detect the groups with values of severe deficiency (< 0.35 μmol/L or < 10 μg/dl), moderate marginal (0.35 μmol/L ≤ 0.70 μmol/L or 10 μg/dl ≤ 20 μg/dl) and doubtful values (0.70 μmol/L ≤ 1.05 μmol/L or 20 μg/dl ≤ 30 μg/dl). The cutoff utilized to indicating inadequacy of serum values of β-carotene was £ 40 μg/dL, as suggested by Sauberlich et al.[22]
- *Oxidative Stress:* Thiobarbituric acid-reactive substances (TBARS) were measured by the method described by Ohkawa et al.[23]
- *C-Reactive Protein (CRP):* It was assessed through the method of nephelometry.

Statistical Analysis

Measures of central tendency and dispersion were calculated. Pearson and Spearman correlations were performed according to each variable behavior, adopting as strong correlation values higher than 0.6, and regular correlation from 0.3 to 0.6. Student "t" and Mann-Whitney tests were applied for comparison of continuous variables. To assessing association between categorical variables, Chi-square (C^2) was applied. The significance level of 5% of probability ($P \leq 0.05$) was adopted. Statistical analysis was performed through the statistical program SPSS for Windows (version 13; SPSS INC., Chicago, IL, USA).

Results

Forty-six individuals were studied. In the act of enrollment in this study, it was observed that 52.2% (n = 24) of the patients received enteral diet, whereas 47.8% (n = 22) were without nutritional support. The collection of the patients with nutritional support occurred between Day 2 and Day 4 after they received the diet and the supplement (the patients had received the 90 to 100% their nutritional needs and regarding the supplement of vitamin A, the dose was full from the entrance of the patient). Among those who were without nutritional support, the time ranged from 24 to 72 hours. There was no report of diarrhea in any of the patients enrolled.

The general characteristics are shown in table I.

As regards the serum concentrations of retinol, it was observed that 39.1% of the patients (n = 18) presented severe deficiency, 15.2% (n = 7) marginal deficiency, 10.9% (n = 5) doubtful values, and 34.8% (n = 16) presented normal concentrations (>1.05 μmol/L). As regards β-carotene, it was observed an inadequacy of 73.9% (n = 34).

Table I
General characteristics

	Nutritional support	*Without support*
n	24	22
Age (years) ± SD	64.2 ± 19.9	65.3 ± 19.2
Sex (M/F)	8/16	12/10
APACHE II ± SD	15.6 ± 3.1	16.7 ± 5.9
Predicted Mortality (%)	25	25

SD: standard deviation; M: male; F: female; APACHE II: Acute Physiology and Chronic Health Evaluation II

It was observed that the inadequacy of retinol and b-carotene was more frequent (77% ; n = 23 and 74%; n = 25, respectively) in patients with higher circulating levels of TBARS (allocated in the 50th and 75th quartiles), however no statistical significance was presented (p = 0.58 and p = 0.39, respectively).

It was not found a relationship among the continuous variables studied, except as regards age and APACHE II score which were positive and significantly correlated (p = 0.009 and r = 0.381).

Patients with adequate retinol presented high frequency of inadequate β-carotene (62.5%), even without statistical significance (p = 0.29).

Among the patients who presented lower concentrations of CRP (allocated in the 25th quartile) it was found a higher β-carotene inadequacy (64.8%) and 50% of retinol inadequacy.

Mean offer of vitamin A was 8,622 ± 4,090 IU/day, corresponding to 288% of the value of the recommended daily dietary intake (DRI)[21] (fig. 1).

Proportion of serum inadequacy of retinol in the groups with and without diet was 54% (n = 13) and 77% (n = 17), respectively, 62.5% (n = 15) of β-carotene in the group with diet, and 86% (n = 19) in the group without diet.

There was no significant difference between the groups with and without diet as regards the mean serum retinol concentrations, TBARS and APACHE II score, differently from what occurred as regards serum concentrations of β-carotene and of CRP (table II).

Discussion

The present study conducted an assessment of the nutritional status of vitamin A and oxidative stress in individuals admitted in ICU with sepsis, aiming to contribute to the review of the nutritional support addressed to this group, with emphasis on the intake of vitamin A.

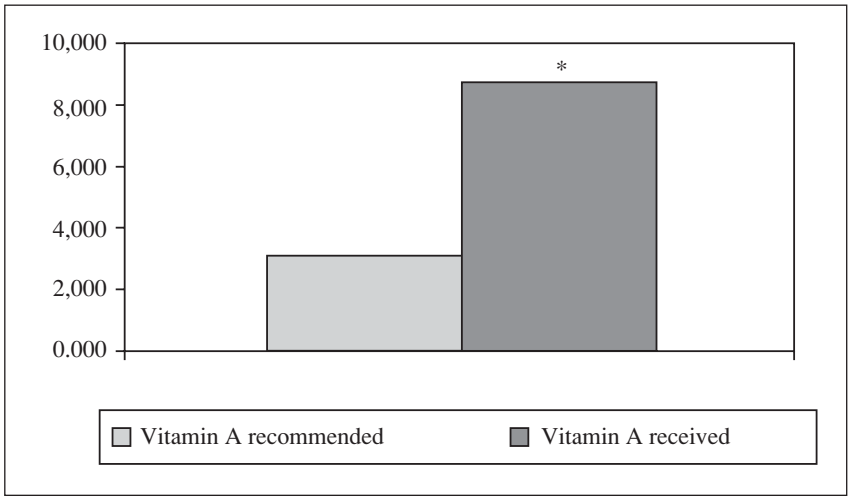

*Fig. 1.—Mean offer of vitamin A of septic patients and recommended dietary intake[15] (*p < 0.05).*

One of the factors which may lead to vitamin A deficiency (VAD) is the frequency of infectious episodes. Nowadays it is known that even subclinical VAD (when Xerophthalmia signs are absent) intensifies the severity of infirmities and of several infectious processes, and it may provoke immunodeficiency status of an exclusively nutritional origin[21] added to a higher metabolic utilization of vitamin A against oxidative stress to which individuals with infectious processes are more exposed to.[1]

In the group studied, besides the high prevalence of deficiency of retinol and β-carotene found, it was observed evidences of lipid peroxidation associated with high CRP, which jeopardizes the clinical condition of the septic patients assessed in a more intense way.

The hypercatabolic status derived from the septic status increases the demand of antioxidant vitamins as vitamin A. Low organic levels of this vitamin may contribute to sepsis aggravation, mainly when other conditions of risk are added as, for example, advanced age.[2]

In the present study an association of APACHE II score was found with age, which could possibly be explained by the fact that the referred score attributes a higher score according to increase of age. Aging may be related to an infectious status aggravation by compromising organ functions, and by all consequences that normally accompany this process.[24]

In the present study, it was observed high mean values of CRP compatible with the inflammatory systemic response and existence of infectious process. This finding corroborates others presented by Andriolo et al[9] who observed similar levels of this marker (146.1 mg/L) in the serum of septic patients who evolved to death. The same was pointed out by Castelli et al[25] who assessed the serum concentrations of CRP in patients with SIRS, sepsis and trauma, finding a mean of 150 mg/L of CRP in the group of septic patients.

A statistical difference (p = 0.001) was observed when the mean serum concentrations of CRP of the groups with and without diet were compared. Concentrations of CRP significantly higher in the group without diet may be related to the very absence of nutritional support whose impact would contribute to the increase of the catabolic demand.

Among the patients who presented lower concentrations of CRP, higher inadequacy of β-carotene was

Table II
Mean values of serum concentrations of retinol, β-carotene TBARS, CRP and APACHE II of patients with sepsis, according to nutritional support

	Retinol (mmol/l)		*β-carotene (μg/dl)*		*TBARS (mmol/ml)*		*CRP (mg/l)*		*APACHE II*	
Nutritional support	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
n	24	22	24	22	24	22	24	22	24	22
Mean	1.03	0.85	44.98	30.27	3.59	5.46	81.20	195.65	15.58	16.73
SD	1.02	1.15	47.04	28.89	3.41	5.34	77.38	114.88	3.13	5.95
p	0.33		0.047*		0.24		0.001*		0.43	

SD: standard deviation; CRP: C-reactive protein; TBARS: reactive substances to thiobarbituric acid; APACHE II: Acute Physiology and Chronic Health Evaluation.
* p < 0.05 considered statistically significant.

found, and half of them presented retinol inadequacy. Data of the National Health and Nutrition Examination Survey in the USA (NHANES III) showed that individuals with values of CRP higher than 10 mg/L presented risk of VAD up to 8.6 times more than individuals with normal inflammatory activity. VAD has already being described as a risk factor for mortality in a large number of infectious diseases.[26] The most consensual justification is that the presence of infections would increase the organic utilization of vitamin A, thus causing firstly a decrease in the serum levels of retinol, which would promote depletion of the liver stores of this micronutrient. On the other hand, VAD associates with damage in the immunological response creating more susceptibility to infections, therefore generating the cycle "infection, deficiency, infection". Such statements may in part explain the increase of severity and mortality in the presence of the status of deficiency of vitamin A.

It is important to point out the findings related to urinary retinol loss associated with infectious processes.[27] Stephensen et al[28] conducted a study with 29 patients in ICU who presented pneumonia or sepsis, and they found an increase in the urinary excretion of retinol in the group studied when compared to healthy individuals. The patients presented an APACHE II score of 18 ± 7 in the first 24 hours of admission to the ICU (a finding similar to the values found in the present study: 16.13 ± 4.68). It was observed that the most severe patients (score > 20) excreted 10 times more retinol than those who were the less severe ones ($p < 0.0022$). Neves et al[29] observed a strong correlation between low serum levels of retinol and higher urinary loss of this nutrient in individuals with infection. Such findings must be taken into account in the understanding of the physiopathological mechanisms related to the development of VAD in patients with infection, mainly during severe infectious processes.

Goode et al[2] studied 16 patients interned in an ICU with a diagnosis of septic shock and secondary organ dysfunction and they found evidences of oxidative stress, as well reduced values of vitamins A and E, and carotenoids (lycopene and β-carotene). Mean serum retinol found was 26.5 µg/dl, mean APACHE II score was 16.6, and the concentrations of TBARS showed a strong negative correlation with those of serum retinol ($p < 0.01$). In the present study, mean retinol was 0.95 µmol/L (27.14 µg/dl) and mean APACHE II was 16.13, results similar to the study previously cited; however it was not found an association between serum levels of TBARS and blood retinol. It was observed that retinol and β-carotene inadequacy was more frequent in patients with higher circulating levels of TBARS (allocated in the 50th and 75th quartiles), nonetheless, no statistical significance was found. All patients studied by Goode et al[2] presented β-carotene inadequacy. Such findings are in agreement with the high serum β-carotene inadequacy observed in the present study.

In the present study, it was not found a statistical difference as regards serum levels of retinol, TBARS and APACHE II score in the groups with and without diet. Up to the present moment, literature does not present results similar to those of the present study, which would enable comparisons with these findings.

As regards β-carotene, it was observed serum concentrations significantly lower in the group without diet. β-carotene is considered provitaminic forms on account of their capacity of bioconversion to retinol, which is the active form of vitamin A. They are formed by an extensive conjugated system of double binds, and are five times more efficient than retinoids as regards protection against oxidative stress.[15] According to Mecocci et al,[30] the adequate nutritional status of vitamin A reduces the conversion of carotenoids into retinol, hence demonstrating that there is a relationship between the nutritional status of retinol and carotenoids. In the present study, besides a reduction of β-carotene in the group without diet, it was verified that individuals with adequate serum concentrations of retinol presented a higher frequency of inadequacy of β-carotene. Such factors could be explained by the mobilization of β-carotene as antioxidants in the fight against oxidative stress (which was higher in the group without diet), and by bioconversion in order to maintain serum retinol concentrations that, despite the inadequate concentrations for the assemblage of patients, did not present statistically significant difference between patients with and without nutritional support. These findings demonstrated that critical patients with sepsis, included in the present study and who did not receive the diet, would be prevented from the antioxidant power of β-carotene taking into account the lower mean serum concentrations found in this subgroup.

Dietary Reference Intake (DRI) of vitamin A for adults is 900 µg/day (males) and 700 µg/day (females) and the UL (Tolerable Upper Intake Level) is 3,000 µg/day.[15]

In the present study, the mean vitamin A administered to patients was 8,622 IU, corresponding approximately to three times the recommended intake for adults;[15] therefore suggesting that the dose of vitamin A routinely offered to these patients was not able to meet the demand of this group, due to the high frequency of serum inadequacy of retinol and β-carotene found in the study.

Conclusion

Septic patients presented an important inadequacy of retinol and β-carotene. The results found in the present study brought elements to the elaboration/review of the nutritional protocol addressed to the group studied, especially as regards the intake of vitamin A as a means of improving the prognosis and evolution of these patients.

Acknowledgments

We want to thank Dr. Guilherme Aguiar, Dr. Carlos Guida (Laboratório Santa Therezinha de Análises e Pesquisas Clínicas LTDA), the General and Medical Board of HSVP, ICU Team and Laboratory of HSVP, ICU of HUCFF, Fátima Bastos, Mauro Baldanza, Juliana Barreto, Andréa Cardoso, Marina Gribel and all members of the team of the Vitamin A Research Group/UFRJ.

References

1. Crimi E, Sica V, Williams-Ignarro S et al. The role of oxidative stress in adult critical care. *Free Radic Biol Med* 2006; 40: 398-406.
2. Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. *Crit Care Med* 1995; 23: 646-651.
3. Bernard GR, Vincent JL, Laterre PF et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.
4. Annane D, Bellisante E, Cavaillon JM. Septic Shock. *Lancet* 2005; 365: 63-78.
5. Taylor DE, Piantadosi CA. Oxidative Metabolism in Sepsis and Sepsis Syndrome. *J Crit Care* 1995; 10: 122-135.
6. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention. *JAMA* 2007; 297: 842-857.
7. Hargraves WA, Hentall ID. Analgesic effects of dietary caloric restriction in adult mice. *Pain* 2005; 114: 455-461.
8. Roth E, Manhart N, Wessner B. Assessing the antioxidative status in critically ill patients. *Curr Opin Clin Nutr Metab Care* 2004; 7: 161-168.
9. Andriolo A, Costa RP, Novo NF. Pró-calcitonina e proteína C reativa em processos infecciosos graves. *J Bras Patol Med Lab* 2004; 40: 169-174.
10. Akobeng AK, Richmond K, Miller V, Thomas AG. Effect of exclusive enteral nutritional treatment on plasma antioxidant concentrations in childhood Crohn's disease. *Clin Nutr* 2007; 26: 51-56.
11. Quasim T, Mcmillan DC, Talwar D, Sattar N, O'Reilly J, Kinsella J. Lower concentrations of carotenoids in the critically ill patient are related to a systemic inflammatory response and increased lipid peroxidation. *Clin Nutr* 2003; 22: 459-62.
12. Halliwell B. Antioxidant characterization. Methodology and mechanism. *Biochem Pharmacol* 1995; 49: 1341-1348.
13. Berger MM. Can oxidative damage be treated nutritionally? *Clin Nutr* 2005; 24: 172-183.
14. Meydani SN, Wu D, Santos MS, Hayek MG. Antioxidants and immune response in aged persons: overview of present evidence. *Am J Clin Nutr* 1995; (Supl. 6): 1462S-1476S.
15. IOM-Institute of Medicine. Vitamin A, In National Academic Press(ed): Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, 2001, pp. 82-161.
16. Gray A, McMillan DC, Wilson C, Williamson C, O'Reilly DSJ, Talwar D. The relationship between the acute changes in the systemic inflammatory response, lipid soluble antioxidant vitamins and lipid peroxidation following elective knee arthroplasty. *Clin Nutr* 2005; 24: 746-750.
17. Stahl W. Lipid oxidation and antioxidants. *Curr Opin Clin Nutr Metab Care* 2000; 3: 121-126.
18. Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250-1256.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818-829.
20. Talwar D, Ha TK, Cooney J, Brownlee C, O'Reilly DS. A routine method for the simultaneous measurement of retinol, alpha-tocopherol and five carotenoids in human plasma by reverse phase HPLC. *Clin Chim Acta* 1998; 270: 85-100.
21. World Health Organization/WHO. Indicators for assessing Vitamin A deficiency and their application in monitoring and evaluating intervention programmes. Micronutrient Series WHO/NUT.10 Geneva: 66, 1996.
22. Sauberlich HE, Hodges RE, Wallace DL, et al. Vitamin A metabolism and requirements in the human studied with the use of labeled retinol. *Vitam Horm* 1974; 32: 251-275.
23. Ohkawa H, Oshishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem* 1979; 95: 351-358.
24. Ausman LM & Russel M. Nutrição do idoso. In Shills ME, Ed. Tratado de Nutrição Moderna na Saúde e na Doença, 9th edn. São Paulo: Manole, 2003: 931-944.
25. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* 2004; 8: R234-R242.
26. Tang AM, Graham NM, Semba RD, Saah AJ. Association between serum vitamin A and E levels and HIV-1 disease progression. *AIDS* 1997; 11: 613-620.
27. Jordäo Jr AA, Figueiredo JFC, Silveira S, Franco MVMJ, Vannucchi H. Excreção urinaria de vitamina A e substâncias reativas ao acido tiobarbitúrico em pacientes com AIDS. *Rev Hosp Clin Fac Med Univ São Paulo* 1998; 53: 11-15.
28. Stephensen CB, Alvarez JO, Kohatsu J, Hardmeier R, Kennedy JI, Gammon RB. Vitamin A is excreted in the urine during acute infection. *Am J Clin Nutr* 1994; 60: 388-392.
29. Neves FF, Vannucchi H, Jordão Jr AA, Figueiredo JF. Recommended dose for repair of serum vitamin A levels in patients with HIV infection/AIDS may be insufficient because of high urinary losses. *Nutrition* 2006; 22: 483-489.
30. Mecocci P, Polidori MC, Troiano L et al. Plasma antioxidants and longevity: a study on healthy centenarians. *Free Radic Biol Med* 2000; 28:1243-1248.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):318-325
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Publicidad y alimentación: influencia de los anuncios gráficos en las pautas alimentarias de infancia y adolescencia

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Resumen

Antecedentes: **Una alimentación óptima, especialmente durante la infancia y adolescencia, es un importante objetivo social, ya que se crean hábitos y conductas alimentarias que se mantendrán durante la vida adulta.**

Objetivo: **El objetivo de este estudio es recoger y valorar la publicidad de alimentos dirigida a un público infantil, antes de la aprobación del código de autorregulación de la publicidad e alimentos dirigida a menores, prevención de la obesidad y salud (Código PAOS) y después de su puesta en marcha.**

Ámbito, material y métodos: **S e visionaron y se recogieron datos de los anuncios de alimentos emitidos por televisión en horario de programación infantil.**

Resultados: **Los resultados obtenidos expresan una gran discrepancia entre la dieta compuesta por los alimentos anunciados y una dieta normal recomendada para niños, así como la ausencia de modificaciones en la publicidad tras la entrada en vigor de dicho código.**

Conclusión: **Los alimentos hipercalóricos ofertados a menores en los espacios publicitarios de la programación infantil no son los adecuados para una dieta óptima. La puesta en marcha del Código PAOS no ha tenido mucha repercusión sobre la cantidad y la calidad de los anuncios de alimentos destinados al público infantil.**

(*Nutr Hosp*. 2009;24:318-325)

Palabras clave: *Publicidad. Conducta alimentaria. Infancia. Obesidad infantil.*

ADVERTISING AND FEEDING: INFLUENCE OF GRAPHICAL ADVERTISEMENTS ON DIETARY HABITS DURING CHILDHOOD AND ADOLESCENCE

Abstract

Background and objectives: **An optimal nutritional diet, especially during the infancy and adolescence, is an important social objective, to create habits and behaviours that will maintain during the adult life of the present children.**

The objective of this study is to collect and evaluate the publicity of nutritional products and how this is directed to children, before the approval of the codex of regulation of teh publicity of nutritional products as directed to minors, prevention of obesity and health (codex PAOS) and after the start of the codex.

Setting, materials and methods: **To watch and collect data from commercials of nutritional products, such as transmitted by television during the infant programs.**

Results: **The obtained results show a great discrepancy between the diet constituted by the commercials for nutritional products and a diet, normally recommended for children. Besides this, nos changes in the commercials were noticed after the start of the codex.**

Conclusion: **The commercials for nutritional products with a very high caloric value are transmitted to children durign the infant programs are not appropiate for an optimal diet. The start of the Codex PAOS did not have much effect in the amount and quality of the commercials of nutritional products, such as directed to the infant public.**

(*Nutr Hosp*. 2009;24:318-325)

Key words: *Publicity. Food habits. Infancy. Infant obesity.*

Introducción

La prevalencia de la obesidad (especialmente en la infancia, donde alcanza cifras alarmantes) y su tendencia ascendente durante las dos últimas décadas, han hecho que en España se afiance el término de "obesidad epidémica". La obesidad infantil se sitúa ya en el 13,9%, y la del sobrepeso está en torno al 12,4%. La cifra mayor se detecta en la prepubertad, en concreto, en el grupo de edad de 6 a 12 años, con una prevalencia del 16,1%[1]. El cambio de hábitos alimentarios y la poca actividad física son, según el Ministerio de Sanidad y Consumo, las principales causas de este espectacular incremento. La Organización Mundial de la Salud la ha calificado como la "Epidemia del Siglo XXI"[2-4]. En la actualidad, existe evidencia científica de que los factores de riesgo de enfermedades crónicas se establecen

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Recibido: 5-IX-2008.
Aceptado: 30-I-2009.

durante la infancia y la adolescencia. La adopción de un estilo de vida saludable parece deseable desde edades tempranas, existiendo en consenso cada vez mayor hacia la prevención[5]. Sería necesario, y de suma importancia, el conocimiento de los factores que condicionan la configuración de los hábitos alimentarios tanto en la infancia, como en la adolescencia[6]. Aunque el conocimiento no siempre condiciona el hábito, puede ser el primer paso para mejorar la dieta[7].

La alimentación es una acción compleja regulada por mecanismos fisiológicos y psicológicos[8] siendo la publicidad uno de los componentes de esos aspectos psicológicos. La publicidad nos influye mucho como consumidores, es uno de los factores más importantes para la venta de un producto[9]. La capacidad de persuasión de la publicidad es tan reconocida que para controlarla se han elaborado numerosas normativas, leyes gubernamentales y acuerdos de autorregulación voluntarios. Dentro de estos últimos, cabe destacar "El código de autorregulación de la publicidad de alimentos dirigida a menores, prevención de la obesidad y salud" (Código PAOS)[10] que entró en vigor el 15 de septiembre de 2005. Este código se encuentra inscrito dentro del marco de la Estrategia NAOS (Estrategia para la Nutrición, Actividad Física y Prevención de la obesidad[11] lanzada recientemente por el Ministerio de Sanidad y Consumo para disminuir la prevalencia de la obesidad y sobrepeso y sus consecuencias. Promovido por la FIAB (Federación de Industrias de Alimentos y Bebidas) tiene el fin de establecer un conjunto de reglas que guíen a las compañías adheridas en el desarrollo, ejecución y difusión de sus mensajes publicitarios dirigidos a menores[12].

Los niños son el grupo social más sensible a los estragos de la publicidad, llegando en muchos casos a convertirse en dependientes del mercado del consumo[13]; de ahí que en los últimos años haya ido incrementándose la preocupación y el interés sobre la relación entre publicidad-edad infantil así como la responsabilidad que se puede derivar de la influencia que en ellos ejerce. La publicidad intenta crear y consolidar en el menor nuevos hábitos de consumo, puesto que son la mejor garantía de tener consumidores en el futuro; explotando las formas de comportamiento social de los niños y la tendencia infantil a imitar los modelos de conducta[13].

La mejor plataforma para hacer llegar a los niños el mensaje publicitario es la televisión, dado que la mayoría de los niños ve la televisión a diario, ocupando una gran parte del tiempo destinado a la diversión[14]. Por otra parte, este medio de comunicación es de baja participación[15], es decir, el niño recibe el mensaje y lo admite sin apenas reflexión, siendo procesada la información por el hemisferio derecho del cerebro, fomentando la pasividad[16]. Otro hecho destacable y demostrado es que los niños tienden a difuminar y disminuir las diferencias entre la publicidad y los programas normales[17,18]. Así, los spots publicitarios dirigidos a menores suelen ofrecer junto con la compra otros productos como pegatinas,... todo ello unido a un gran soporte de medios audiovisuales que inducen a comprar. La fascinación infantil por los colores llamativos, regalos promocionales o personajes fantásticos que prometen sabores irrepetibles, subyugan al incipiente consumidor al poder del anuncio y, por consiguiente, al del alimento en cuestión. Tal como explica Joan Ferrés[19], la publicidad es el máximo exponente de un juego de engaños.

Un gran porcentaje de estos anuncios ofertados en televisión corresponde a productos alimentarios y dada la posible influencia de la publicidad en los niños, los hábitos alimentarios infantiles pueden estar, en parte, condicionados por la publicidad. La relación entre estos tres factores: alimentación, publicidad e infancia, es el objetivo de este estudio, mediante la observación directa de la publicidad de productos alimentarios ofertada en la televisión, en horario infantil, antes de la aprobación del Código PAOS y después de su puesta en marcha. Con los resultados obtenidos se hará una comparación entre los alimentos que se ofertan y los que compondrían una dieta óptima, además de valorar si se ha modificado la cantidad o características de la publicidad alimentaria dirigida al público infantil después de la entrada en vigor del Código PAOS.

Material y métodos

Población a estudio

Analizar la publicidad y los contenidos de los anuncios de alimentos dirigidos al público infantil, con edades comprendidas entre los 3 y los 12 años, es el objeto de este estudio. Es importante establecer unos márgenes de edad tanto para limitar los que se consideran anuncios destinados al público infantil, como para determinar la que se considera alimentación normal o adecuada de dicha población.

Material

El medio de comunicación elegido como vehículo de la publicidad alimentaria destinada a menores es la televisión. Los criterios de selección seguidos son evaluar los anuncios de alimentos emitidos durante la programación destinada al público infantil en días escolares y en las cadenas de televisión con mayor audiencia de las de cobertura nacional y gratuita. Se redujo el campo a la programación infantil vespertina ofertada por TV2, un espacio de tiempo comprendido entre las 17:30 a 19:10 en el año 2005. En el año 2007, se tomó como base para el estudio la programación infantil ofertada por la TV2 a medio día, de 13:30 a 15:00, ya que la vespertina se consideró dirigida a un público adolescente. En concreto se trabajó sobre una semana escolar de mayo de 2005 (viernes 6, lunes 9, martes 10, viernes13 y el lunes 16) y una semana escolar de mayo-

junio de 2007 (martes 29, miércoles 30, lunes 11, martes 12 y jueves 14) El hecho de no poder coger semanas completas y tener que trabajar sobre días de diferentes semanas se debe a que los días 11 y 12 de mayo de 2005 la programación habitual de la TV2 fue cancelada por la emisión del *Debate sobre el Estado de la Nación* y la programación infantil de finales de mayo, principios de junio de 2007 se vio suspendida por la emisión del *Torneo de Roland Garros*.

Método de estudio

El estudio consistió en la observación directa de la programación de televisión infantil, registrando los anuncios ofertados y los tiempos de emisión destinados a los mismos en hojas de recogida de datos diseñadas a tal fin.

Análisis estadístico

Tras el estudio descriptivo, se calcularon medias y desviaciones de los datos mediante la aplicación SPSS 11.

Resultados y discusión

La publicidad de alimentos emitida en horario programación infantil, durante los días escolares, queda reflejada en los siguientes datos:

La programación infantil vespertina en el año 2005 durante los días escolares se limitaba a "Los lunnis" que solía empezar su emisión sobre las 17:30 y acabar a las 19:10. En el año 2007 la programación infantil emitida a medio día suele empezar a las 13:30 y acabar a las 15:00 (tablas I y II).

En el espacio de tiempo comprendido entre las 17:30 y las 19:10 de 2005 habitualmente se incluían 4 sesiones de anuncios. En el año 2007, en la programación infantil ofertada entre las 13:30 y las 15:00 hay 3 sesiones de anuncios (tablas I y II).

En 2005 el tiempo medio dedicado a esos anuncios era de 5 minutos cada sesión. En 2007 el tiempo aumenta hasta una media de 7 minutos por sesión. El porcentaje del tiempo que ocupan los anuncios del total de minutos de la programación infantil observada en esos cinco días era el 18,4% en 2005. En 2007 es del 23,5%, lo cual implica también un aumento del tiempo destinado a anuncios (fig. 1).

En 2005 cada sesión de anuncios se componía de una media de 14 anuncios, de los cuales el 32% es publicidad de productos alimenticios. En 2007 hay una media de 25 anuncios por sesión, de los cuales el 31% se destina a productos alimenticios (fig. 2). La cantidad total de anuncios de alimentos se ha incrementado un 48% entre los dos años estudiados.

En 2005 se observó una forma de reclamo que parece especialmente perjudicial para el niño: asociar la ingesta de un determinado alimento con "ser el mejor". Un anuncio dice literalmente "si no eres el mejor es porque no quieres", en el contexto de un niño mal deportista que consigue muchos amigos/admiradores cuando come un determinado tipo de galletas.

En ambos periodos los alimentos más ofertados son galletas, cereales de desayuno, lácteos, helados, bollería, batidos, cacao y golosinas. Las figuras 3 y 4 reflejan el total de anuncios de alimentación observados agrupados en función del producto que ofertan. En ambos casos la mayoría de los anuncios de alimentos contienen imágenes en dibujos animados y muchos ofrecen regalos por la compra de los productos.

En ambos años los alimentos que se ofertan son muy energéticos y de poco valor nutritivo, generalmente ricos en azúcares simples y grasas. En ambos años no

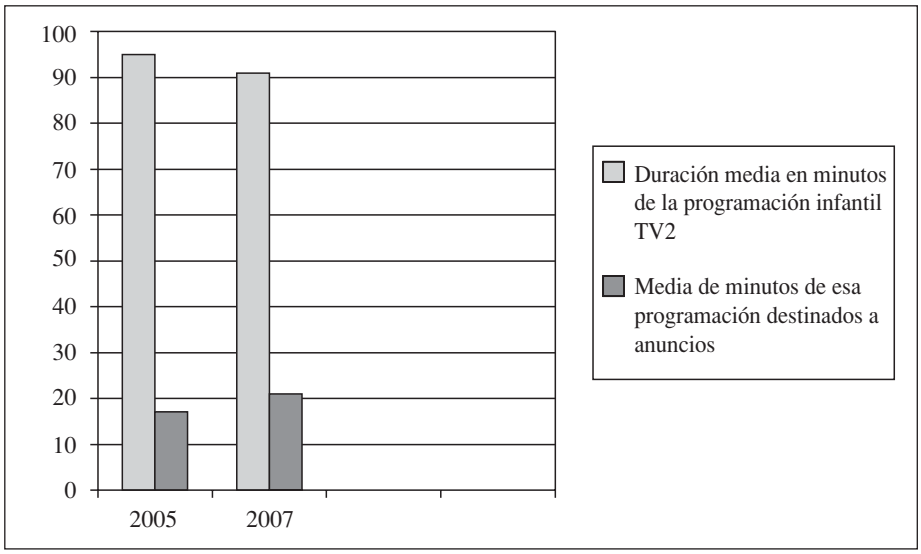

Fig. 1.—Tiempo medio diario en minutos invertidos en la programación infantil, vespertina en 2005 y a medio día en 2007, de TV2 durante las semanas de estudio y tiempo de esa programación destinado a anuncios.

Tabla I

Programación infantil y anuncios observados en la programación infantil vespertina de TV2 durante una semana escolar de mayo de 2005

Viernes 6 de mayo		*Lunes 9 de mayo*		*Martes 10 de mayo*		*Viernes 13 de mayo*		*Lunes 16 de mayo*	
17:40	"Los Lunnis"	17:30	"Los Lunnis" y en segundos pasan a anuncios, 5 minutos TAE: 6 AA: 3 (galletas, yogur, cereales)	17:33	"Los Lunnis" y en un minuto los anuncios: 5 minutos TAE: 15 AA: 4 [galletas (2), batido, cereales]	17:34	"Los Lunnis" y en breves segundos los anuncios: 5 minutos TAE: 14 AA: 5 [galletas (2), bollería, cereales, golosinas]	17:29	"Los Lunnis"
17:43	"Tommy y Oscar"**	17:35	"Tommy y Oscar"	17:38	"Tommy y Oscar"	19:39	"Tommy y Oscar"	17:33	Anuncios: 4 minutos TAE: 13 AA: 4 (galletas, yogur, bollería, golosina)
18:04	Anuncios: 7 minutos TAE: 25 AA: 13 [golosinas (2), cereales (3), galletas (2), bollería (3), yogur, agua, "fast food"]	17:57	"Los Lunnis"	18:04	Anuncios: 5 minutos TAE: 14 AA: 4 (yogur, cereales, galletas, golosinas)	18:37	Anuncios: 6 minutos TAE: 18 AA: 7 ["fast food", galletas, golosinas (2), yogur, cereales (2)]	17:37	"Tommy y Oscar"
18:11	"Los Lunnis"	18:04	"Los Lunnis"	18:09	"Los Lunnis"	18:10	"Los Lunnis"	18:01	Anuncios: 6 minutos TAE: 19 AA: 7 [galletas (3), cereales, golosinas (2), yogur]
18:37	"Las tres mellizas"**	18:37	Anuncios: 5 minutos TAE: 16 AA: 4 [galletas (2), cereales, golosina]	18:36	Anuncios: 4 minutos TAE: 11 AA: 5 [galletas (3), cereales, golosinas]	18:36	Anuncios: 3 minutos TAE: 7 AA: 2 (golosina, yogur)	18:07	"Los Lunnis"
19:04	Anuncios: 6 minutos TAE: 19 AA: 7 [cereales, batido, galletas (2), bollería, yogur, cacao en polvo]	18:09	"Los Lunnis"	18:40	"Las tres mellizas"	18:39	"Las tres mellizas"	18:32	Anuncios: 5 minutos TAE: 14 AA: 5 (golosinas, galletas, cacao en polvo, cereales, batido)
19:10	Fin de "Los Lunnis"	18:34	Anuncios: 4 minutos TAE: 11 AA: 3 (golosina, cereales, galletas)	19:05	"Los Lunnis"	19:05	Anuncios: 5 minutos TAE: 13 AA: 4 (bollería, galletas, golosinas, yogur)	18:37	"Las tres mellizas"
		18:38	"Las tres mellizas"	19:07	Anuncios: 5 minutos TAE: 14 AA: 3 [galletas (2), cereales (1)]	19:10	Fin de "Los Lunnis"	19:03	Anuncios: 5 minutos TAE: 16 AA: 2 (galletas)
		19:04	"Los Lunnis"	19:12	Fin de "Los Lunnis"			19:08	"Los Lunnis"
		19:05	Anuncios: 5 minutos TAE: 13 AA: 3 (galletas, batido, yogur)					19:10	Fin de la programación infantil
		19:10	Fin de "Los Lunnis"						

*: Programa infantil que a su vez incluye dos series de dibujos animados.
**: Serie infantil de dibujos animados.
TAE: Número **T**otal de **A**nuncios **E**mitidos en una tanda de anuncios.
AA: Número total de **A**nuncios de **A**limentos durante esa tanda de anuncios.

Tabla II

Programación infantil y anuncios observados en la programación infantil de TV2 durante una semana escolar de mayo de 2007

Martes 29 de mayo		*Miércoles 30 de mayo*		*Lunes 11 de junio*		*Martes 12 de junio*		*Jueves 14 de junio*	
13:32	"Lola y Virginia"	13:41	Anuncios: 7 minutos TAE: 23 AA: 7 (cacao en polvo, helado, queso, paté, golosinas, galleta, cacahuetes con chocolate)	13:35	Anuncios: 8 minutos TAE: 30 AA: 10 [golosinas (2), cacao en polvo (3), batido, helado, yogur, paté]	13:29	Anuncios: 8 minutos TAE: 31 AA: 10 [yogur, helado, golosinas (2), batido (2), cacao en polvo, "fast food"]	13:37	Anuncios: 8 minutos TAE: 29 AA: 9 [helado, batido, baollería, yogur, golosinas, cacao en polvo(2), paté, galletas)
13:34	Anuncios: 7 minutos TAE: 25 AA: 8 [cereales con chocolate, golosinas, paté, galletas, cacao en polvo (2), helado, cacahuetes con chocolate]	13:48	"Lola y Virginia"	13:43	"Lola y Virginia"	13:37	"Lola y Virginia"	13:45	"El año del dragón"*
13:42	Continua "Lola y Virginia"	14:12	Anuncios: 8 minutos TAE: 22 AA: 4 (cereales con chocalate, paté, helado, cacahuetes con chocolate)	14:08	Anuncios: 7 minutos TAE: 26 AA: 7 [galletas, helado, yogur, cacao en polvo (2), paté, golosina)	14:01	Anuncios: 7 minutos TAE: 25 AA: 10 [golosinas, galletas, helado (2), bollería, yogur, cacao en polvo (2), paté, "fast food"]	14:07	Anuncios: 7 minutos TAE: 26 AA: 10 [galletas (2), helados (2), bollería, yogur, "fast food" (2), paté, cacao en polvo]
14:05	Anuncios: 8 minutos TAE: 25 AA: 6 ("fast food", cacao en polvo, queso, paté, galletas, helado)	14:20	"Zatchbell"	14:15	"Zatchbell"	14:08	"Zatchbell"	14:14	"Zatchbell"
14:14	"Zatchbell"*	14:40	Anuncios: 5 minutos TAE: 18 AA: 5 ("fast food", cacao en polvo, golosinas, galletas, cacahuetes con chocolate)	14:36	Anuncios: 6 minutos 30 segundos TAE: 24 AA: 9 [golosinas (2), galletas, helado, cacao en polvo (2), batido (2), paté]	14:28	Anuncios: 8 minutos TAE: 27 AA: 8 [cacao en polvo (2), galletas, helado, yogur, batido (2), paté]	14:34	Anuncios: 6 minutos TAE: 24 AA: 10 [batido, galletas, yogur, cacao en polvo (2), helado, "fast food" (2), paté]
14:34	Anuncios: 9 minutos TAE: 17 AA: 2 (golosinas, "fast food")	14:45	"Las tortugas ninja"	14:42	"Iron Kid"*	14:36	"Iron Kid"	14:40	"Iron Kid"
14:40	"Las tortugas ninja"*	15:07	Fin programación infantil	15:05	Fin programación infantil	15:01	Fin programación infantil	15:05	Fin programación infantil
15:02	Fin programación infantil								

*: Serie infantil de dibujos animados.
TAE: Número **T**otal de **A**nuncios **E**mitidos en una tanda de anuncios.
AA: Número total de **A**nuncios de **A**limentos durante esa tanda de anuncios.

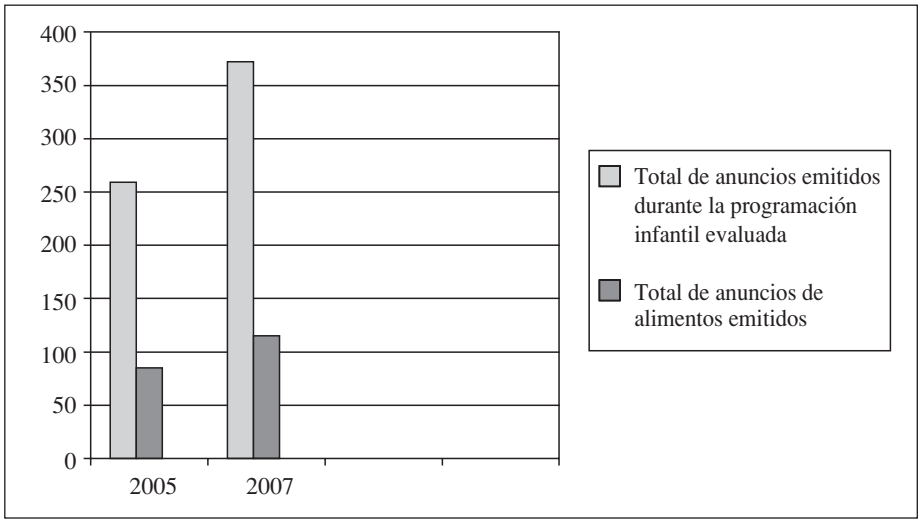

Fig. 2.—Total de anuncios emitidos en los cinco días de programación infantil observada en TV2, vespertina en 2005 y a medio día en 2007, y el total de anuncios emitidos destinados a productos alimentarios.

hay anuncios de frutas, verduras o pescado, de los alimentos que serían la base de una dieta equilibrada. Tampoco se incluyen recomendaciones dietéticas, consejos alimentarios o hábitos de vida saludables.

De los dos puntos anteriores se deduce que la alimentación ofertada es deficitaria en frutas, legumbres, vegetales y pescados y excesiva en grasa y azúcares simples. Hay una divergencia clara entre lo que se ofrece y lo que los expertos en nutrición recomiendan consumir. Afirmación que se refleja en las dos pirámides representadas en la figura 5, la de la izquierda representa la dieta aconsejada y la de la derecha la que compondrían los alimentos anunciados. Resultados que son muy preocupantes si tenemos en cuenta que otro estudio similar realizado entre escolares británicos de primaria[20] demuestra la estrecha relación existente entre la publicidad y el consumo de productos artificiales previamente publicitados, en detrimento de alimentos naturales. Según el estudio, diez de los productos más consumidos por los integrantes de la muestra correspondían a los diez alimentos publicitados con más frecuencia en las pausas de los programas televisivos preferidos por los niños. Tal como ponen de manifiesto los autores, los *spots* de refrescos, de patatas fritas y de bollería fueron los más recordados por la población infantil analizada, datos que concordaron claramente con los productos más consumidos por dicha muestra.

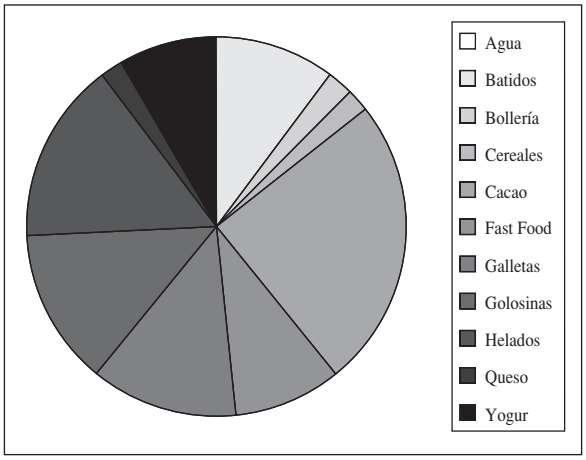

Fig. 4.—Muestra del total de anuncios emitidos en la programación infantil a medio día de TV2 en 2007 los porcentajes que se destinaron a los distintos tipos de alimentos.

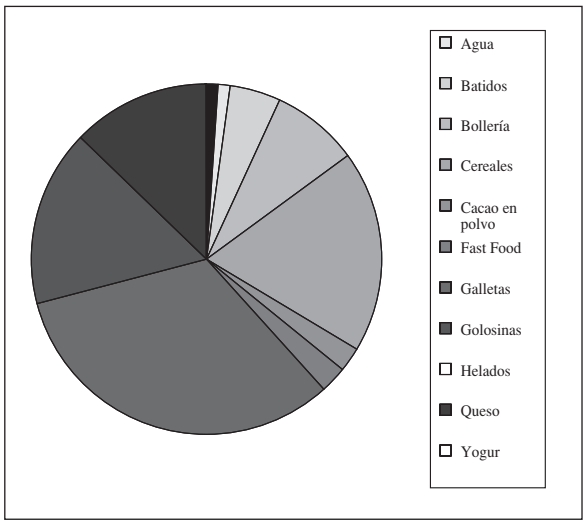

Fig. 3.—Muestra del total de anuncios de alimentos emitidos en la programación infantil vespertina de TV2 en 2005 los porcentajes que se destinaron a los distintos tipos de alimentos.

Del estudio de los anuncios de productos alimentarios emitidos en televisión en horario de programación infantil durante la semana escolar podemos afirmar que el tiempo destinado a publicidad dentro de la programación infantil ha aumentado un 5%. El tiempo destinado a publicidad de alimentos era y continúa siendo, aproximadamente, un tercio del total destinado a publicidad, a lo que hay que sumar que el efecto de la publicidad se ve intensificado

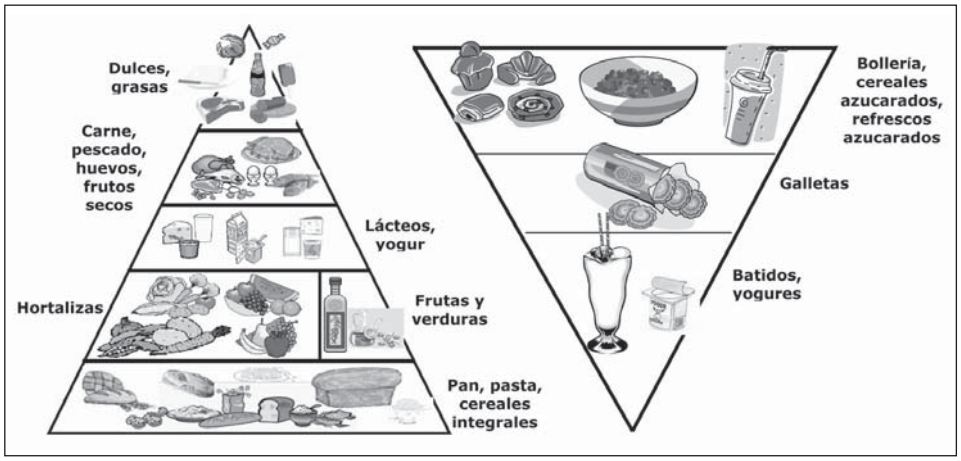

Fig. 5.—Comparación entre la pirámide nutricional aconsejada (a la izquierda, según mayor o menor frecuencia de consumo, de la base a la cúspide) y la pirámide nutricional que saldría con los alimentos ofertados en los anuncios durante la programación infantil (a la derecha).

por el número de horas totales que un niño pasa delante del televisor. Así, según el estudio del *Consell de Audiovisual de Catalunya* realizado en el ámbito autonómico, los menores pasan anualmente 990 horas frente a pantallas electrónicas — la mayoría de ellas ante el televisor— y sólo 960 en la escuela, de ahí que resulte más que evidente señalar la influencia que la televisión ejerce sobre el sedentarismo de este público y, más concretamente, la de la publicidad sobre las tendencias del consumo alimentario de la población infantil[21,22]. Este estudio coincide con nuestro trabajo al destacar que la mayoría de los productos ofertados son dulces, fast food, cereales azucarados, aperitivos salados y refrescos, es decir, alimentos de alto contenido energético y bajo valor nutritivo.

También relativo a la influencia que tiene la publicidad sobre la elección del producto, está el hecho de que la gran mayoría de los anuncios están pensados para la mente infantil, conectando con ellos a través de imágenes que captan su atención, sobre todo de dibujos animados y la utilización de personajes famosos y admirados. En el caso de la animación hay que destacar que si los niños más pequeños no tienen clara la frontera entre programación y anuncios, el alimento así ofertado será como algo propio de la fantasía pero que se puede conseguir.

Respecto a la valoración del efecto del Código PAOS, dentro de la estrategia NAOS, sobre la publicidad dirigida especialmente al público menor de 12 años, resaltamos las normas éticas que, aunque aprobadas, no se están cumpliendo:

Punto 6 de la norma ética III, presentación de los productos: *"En los anuncios de alimentos y bebidas dirigidos a un público menor de edad deben adoptarse precauciones para no explotar la imaginación del menor. La fantasía, incluyendo las animaciones y los dibujos animados, es idónea tanto para niños más pequeños como para mayores. Sin embargo, debe evitarse que la utilización publicitaria de tales elementos cree expectativas inalcanzables o explote la ingenuidad de los niños pequeños a la hora de distinguir entre fantasía y realidad"* Cualquier observador que encienda la televisión en horario infantil puede comprobar que más del 70% de los anuncios incluyen algún tipo de animación, cuando no es el anuncio completo. Esto es claramente destacable en los anuncios de alimentos.

Punto 11 de la norma ética V, presión de ventas: *"En los anuncios de alimentos y bebidas dirigidos a un público infantil los beneficios atribuidos al alimento o bebida deben ser inherentes a su uso. La publicidad no debe dar la impresión de que adquirir o consumir un alimento o bebida dará una mayor aceptación del niño entre sus amigos. Y al contrario, tampoco debe implicar que no adquirir o consumir un producto provocará el rechazo del niño entre sus compañeros"* . El anuncio al que nos referíamos en 2005 como un reclamo especialmente perjudicial ha sido retirado, además, contravenía claramente este punto.

Punto 13 de la norma ética VI, apoyo y promoción a través de personajes y programas: *"La publicidad de alimentos o bebidas en ningún caso explotará la especial confianza de los menores en sus padres, profesores, o en otras personas, tales como profesionales de programas infantiles, o personajes (reales o ficticios) de películas o series de ficción, ni personajes conocidos o famosos de alto grado de aceptación entre el público infantil"* . Este punto sigue sin cumplirse ya que se utilizan deportistas famosos y personajes de dibujos animados (no creados específicamente para el producto,) para promocionar alimentos infantiles.

Punto 17 de la norma ética IX, promociones, sorteos, concursos y clubes infantiles: *"El mensaje publicitario que incluya una promoción deberá diseñarse de tal forma que, además de transmitir el mensaje relativo al incentivo promocional, muestre claramente el producto anunciado"* Como ya hemos dicho hay anuncios donde apenas se ve el alimento, sólo los regalos ofertados.

Conclusiones

Los alimentos hipercalóricos ofertados a menores en los espacios publicitarios de la programación infantil no son los adecuados para una dieta óptima.

La publicidad de alimentos utiliza estrategias a las que los menores son muy sensibles como músicas alegres, colores vivos, personajes de animación o la asociación de un alimento con el éxito social.

La puesta en marcha del Código PAOS no ha tenido mucha repercusión sobre la cantidad y la calidad de los anuncios de alimentos destinados al público infantil.

Los anunciantes y agencias deberían desarrollar estrategias conjuntas para elaborar una publicidad de alimentos educativa, dirigiendo su influencia hacia una alimentación sana, equilibrada y complementada con ejercicio físico.

Referencias

1. Ministerio de Sanidad y Consumo. "Campañas 2007. Prevención de la obesidad infantil" www.msc.es/campannas/campanas06/obesidadInfant3.htm
2. Briz Hidalgo FJ, Cos Blanco AI, Amate Garrido AM. "Prevalencia de obesidad infantil en Ceuta. Estudio PONCE 2005". *Nutr Hosp* 2007; 22 (4): 471-477.
3. WHO. "Obesity and overweight". 2003. http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/
4. WHO. "Obesity: Preventing and Managing. The Global Epidemia". Report of WHO Consultation on Obesity. Geneva. 1998.
5. González-Gross M, Gómez-Lorente JJ, Valtueña J, Ortiz KC, Meléndez A. "The healthy liefstyle guide pyramid for children and adolescents" *Nutr Hosp* 2008; 23 (2):159-168.
6. De Rufino-Rivas P, Redondo Figuero C, Viadero Ubierna MªT, Amigo Lanza T, González-Lamuño D, García Fuentes M. "Aversiones y preferencias alimentarias de los adolescentes de 14 a 18 años de edad, escolarizados en la ciudad de Santander". *Nutr Hosp* 2007; 22 (6): 695-701.
7. Rodríguez-Rodríguez E, Perea JM, Bermejo LM, Marín-Arias L, López-Sobaler AM, Ortega RM. "Hábitos alimentarios y su relación con los conocimientos, respecto al concepto de dieta equilibrada, de un colectivo de mujeres jóvenes con sobrepeso/obesidad". *Nutr Hosp* 2007; 22 (6): 654-60.
8. García Arias MT, García Fernández MC. "Nutrición y Dietética". 2003. Ed Universidad de León.
9. Santibáñez Velilla J. *"Ética en la publicidad de golosinas ante los efectos de algunos de sus aditivos en la salud humana"*. 2005. Universidad de la Rioja.
10. Ministerio de Sanidad y Consumo "Código PAOS", www.autocontrol.es/pdfs/cod_%20paos.pdf
11. Fernández San Juan PM. "Dietary habits and nutritional status of school aged children in Spain" *Nutr Hosp* 2006; 21 (3): 374-378.
12. Ministerio de Sanidad y Consumo. Agencia Española de Seguridad Alimentaria. Estrategia NAOS. www.naos.aesan.msc.es/naos/ficheros/estrategia/estrategianaos.pdf
13. Anónimo. "El poder de la publicidad". 2005. http://www.cnice.mec.es/recursos2/estudiantes/jovenes/op_21.htm p.1
14. Jara L. "¿Qué televisión ven los niños?". 2004. Informe para C.E.A.C.U.
15. Castells Cuixart M. "Nutrición y prensa" Tesis doctoral de la Universidad Complutense de Madrid. Facultad de Farmacia. Departamento de Nutrición y Bromatología. 1996, pp. 65.
16. Schiffman LG. "Comportamiento del consumidor". 2001. Séptima edición. Ed Prentice-Hall Hispanoamericana, S.A. Méjico.
17. Dietz WH. "The obesity epidemic in young children. Reduce television viewing and promote playing". *B Med J* 2001; 322: 313-314.
18. Robertson T, Rossiter R. "Children and comercial persuasión: an attribution theory análisis". *J Con Res* 1974; 1: 13-20.
19. Ferrés J. "Televisión Subliminal. Socialización mediante comunicaciones inadvertidas". 1996. Ed Paidós. Barcelona.
20. Hitchings E, Moynihan PJ. "The relationship between television food advertisements recalled and actual foods consumed by children". *J Nutr Diet* 1998; 11: 511-517.
21. Jiménez M. "Cuando Barbie se come a Garfield. Publicidad y alimentación: niños obesos buscando la perfección del cuerpo adulto". *Trastornos de la Conducta Alimentaria* 2006; 3: 245-263.
22. Consell de l'Audiovisual de Catalunya, CAC. Llibre blanc: l'educació en l'entom audiovisual. Ed.Quaderns del CAC. Número extraordianri. Barcelona. 2003.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):326-332
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Effect of non-steroidal anti-inflammatory drug etoricoxib on the hematological parameters and enzymes of colon and kidney

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Abstract

The present study was designed to investigate the effects of a selective COX-2 inhibitor, etoricoxib in rats on the hematological and toxicity parameters in colon and kidney at two different doses of the drug, one within the therapeutic anti-inflammatory range as based on the reported ED50 value (Eto-1) while the other at ten times higher (Eto-2), relative to the toxicity studies which have not been reported so far. The results showed that the control and the drug treated animals achieved similar linear growth rate and also showed no major alterations in the histological parameters in the liver and kidney tissue. The animals treated with lower dose of etoricoxib showed an overall decrease in total leukocytes counts as well as in the number of neutrophils, lymphocytes, monocytes and eosinophills while the higher dose of the drug produced a highly significant increase in all the cell counts. However, the drug treatment at both the dose level produced significant fall in the activities of alkaline phosphatase, sucrase, lactase and maltase in the kidney but increased the activity of alkaline phosphatase in colon. The treatment of etoricoxib did not produce any change in the nitric oxide and citrulline levels in kidney while an increase was noted in the colonic tissue. It was concluded that etoricoxib is a relatively safe drug at its anti-inflammatory ED50 dose in rats when the hematological parameters and the structural and functional characteristics of kidney and colonic tissues were studied.

(*Nutr Hosp*. 2009;24:326-332)

Key words: *Non-steroidal anti-inflammatory drug etoricoxib. Leukocyte cell counts. Enzymes of rat colon and kidney.*

EFECTO DEL FÁRMACO ANTIINFLAMATORIO NO ESTEROIDEO ETORICOXIB SOBRE LOS PARÁMETROS HEMATOLÓGICOS Y LAS ENZIMAS DEL COLON Y EL RIÑÓN

Resumen

El presente estudio se diseñó para investigar los efectos de un inhibidor selectivo de la COX-2, etoricoxib, sobre los parámetros hematológicos y de toxicidad en colon y riñón de rata, con dos dosis distintas del fármaco, una dentro del rango terapéutico sobre la base del valor ED50 notificado (Eto-1) mientras que la otra fue diez veces superior (Eto-2), relativa a los estudios de toxicidad que aún no han sido publicados. Los resultados mostraron que los animales control y los tratados consiguieron tasas de crecimiento linear similares y no mostraron alteraciones importantes en los parámetros histológicos del hígado o riñón. Los animales tratados con la dosis inferior de etoricoxib mostraron una disminución global del recuento de neutrófilos, linfocitos, monocitos y eosinófilos, mientras que la dosis superior del fármaco produjo un aumento significativo de todos los recuentos celulares. Sin embargo, el tratamiento con el fármaco a ambas dosis produjo una caída significativa de las actividades de la fosfatasa alcalina, sucrasa, lactasa y maltasa del riñón y una actividad aumentada de la fosfatasa alcalina del colon. El tratamiento con etoricoxib no produjo ningún cambio en las concentraciones de óxido nítrico ni de citrulina en el riñón pero sí se observó un aumento en el tejido colónico. Se concluyó que el etoricoxib es un fármaco relativamente seguro a su dosis ED50 antiinflamatoria en ratas cuando se estudiaron los parámetros hematológicos y las características estructurales y funcionales de los tejidos renal y colónico.

(*Nutr Hosp*. 2009;24:326-332)

Palabras clave: *Fármaco antiinflamatorio no esteroideo etoricoxib. Recuentos leucocitarios. Enzimas del colon y riñón de rata.*

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Recibido: 15-IX-2008.
Aceptado: 2-II-2009.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have come to play an important role over the years in pharmacological management of arthritis and pain.[1] NSAIDs are effective in controlling the joint pain and swelling in rheumatoid arthritis and have also shown in recent times to prevent the formation of cancer in different tissues.[2] However, NSAIDs are associated in humans with toxicities such as gastro-intestinal ulcer and bleeding.[3] The anti-inflammatory action of NSAIDs can be explained by their capability to inhibit the synthesis of prostaglandins, particularly to inhibit the cyclooxygenase (COX) enzymes.[4] COX is demonstrated to be existing as three distinct isoforms, COX-1, COX-2 and COX-3.[5] COX-1 is expressed constitutively in human kidney and brain, while its expression is being induced in many tissues during inflammation, normal wound healing and neoplasia.[6] Therefore, it was proposed that the selective COX-2 inhibitors may become more effective and safe chemopreventive agents than classical NSAIDs which preferentially inhibit COX-1.[7] Studies have also shown that the selective COX-2 inhibitors are effective and well tolerated in treatments for rheumatoid arthritis and other inflammatory disorders.[8,9]

Etoricoxib (5-chloro-6-methyl-3-[4-(methyl sulfonyl) phenyl]-2-3'-bipyridine) is a recent entry into the field of selective COX-2 inhibitors that has been developed for treatment of osteoarthritis, rheumatoid arthritis and pain.[10] Etoricoxib, being COX-2 inhibitor, has the therapeutic advantage of decreasing inflammation at the tissue sites particularly in joints, while sparing gastrointestinal mucosa due to continued prostaglandin production via the COX-1 isoform.[11] However, COX-2 enzymes are also expressed at multiple nephron sites in the mammalian kidney including the cortical thick ascending limb, macula densa, medullary interstitial cells and the endothelium of arteries and veins as well as glomerular podocytes.[12] Thus, it is possible that inhibition of COX-2 enzymes may be associated with alterations in renal functions. Also, the expression of COX-2 is increasingly induced during consecutive stages of cancer. The role of this enzyme in colorectal carcinogenesis is well established by Oshima and Taketo[13] showing that COX-2 deficiency partly suppressed the familial adenomatous polyposis and cancers. Thus, the chemopreventive role of COX-2 inhibitors is also a major consideration in their therapeutic dose and being investigated in the present laboratory in experimental colon cancer.[14-18]

In the present study, an attempt has been made to investigate the effect of the COX-2 selective inhibitor, etoricoxib on rat kidney and colon histoarchitecture and enzyme profiles at two different doses, one at within its therapeutic anti-inflammatory range as based on the reported ED50 value for rats while the other at a ten times higher dose which is expected to relate to the toxicity effects. In view of the immunosuppressive response of the drug, the hematological parameters were also studied in the peripheral blood leukocytes.

Materials and methods

The experiments were performed on male Wistar rats of body weights ranging between 135-150 g, obtained from the central animal house of Panjab University. The animals were housed in plastic cages embedded with rice husk and maintained on standard rodent feed, and also had free access to water. The body weights of the animals were recorded weekly in a single pan animal scale. All of the animal procedures as reported here followed the guidelines approved by the Panjab University Ethical Committee on the use of the experimental animals for biomedical research.

A six week study was designed where the animals were divided into three different groups having 6 animals each. Group 1: The animals served as control receiving the daily dose of 0.5% carboxy methyl cellulose sodium salt as vehicle of the NSAID. Group 2: The animals were given a daily oral administration of Etoricoxib at a concentration of 0.64 mg/kg body wt, called Eto-1. Group 3: The animals were given a daily oral administration of Etoricoxib at a concentration of 6 mg/kg body weight, called Eto-2.

At the end of the six weeks duration, the animals were anesthetized with ether and blood collected from the ocular vein with a glass capillary. The animals were thereof sacrificed with an overdose of ether and tissues collected.

Total leukocytes count (TLC) was done following the methods of Dacie and Lewis[19] in blood samples diluted with freshly prepared Turk's solution containing crystal violet stain and using a WBC diluting tube (Thomas White Cell Pipette) with a dilution of 1:20. The cells were then counted in a Neubauer Chamber and using a light microscope. Differential leukocyte count (DLC) was done by the thick smear method of blood followed by Field's stain which contained the stains, Azure A, Methylene blue and Eosin. Eosinophills appeared as bright red, large cells with well defined granules, neutrophils as pale purple pink and small indistinct cells, basophils as deep blue cells with reddish cast while the monocytes were large sized cells with kidney shaped nucleus.

For histopathological studies, small pieces of colon and kidney were taken, washed with ice-cold 0.9% saline and fixed in Bouin's fixative for 24 hours.[20] After fixation, the tissues were processed carefully for paraffin wax (58-60^0 C), embedded in the wax and sections were cut at 5 µM thickness in a microtome. Parrafin sections as taken on an albumin coated glass slides as a continuous ribbon were dewaxed in xylene, down graded (hydrated) in decreasing percentage of alcohols and brought to water, stained with haematoxylin for 20 sec and washed in tap water till the appearance of blue color. The slides were then rinsed in ammonia water,

Table I
Effect of etoricoxib on total and differential leucocyte counts

Groups	*Total leukocyte counts*	*Neutrophils*	*Lymphocytes*	*Monocytes*	*Eosinophils*
Control	7.567 ± 83.33	1.046 ± 64	6.138 ± 144	100 ± 26.33	100 ± 26.33
Etoricoxib 1	5.333 ± 696.02*	762 ± 24.25	4.399 ± 679.14	85 ± 10.97	53 ± 6.96
Etoricoxib 2	11.400 ± 692.82**	8.476 ± 354.99**	9.230 ± 534.58**	148 ± 28.21	114 ± 6.93

Values are mean ± S.E.M. of six independent observations.
* $p < 0.05$.
** $p < 0.01$.

again washed with water and treated with acid water if over stained. The sections were upgraded in alcohol till 70%, stained with 1% alcoholic eosin for 30 sec and differentiated in 90% alcohol (Delafield hematoxylin-eosin technique). The slides were cleaned in xylene and finally mounted in distyrene plasticizer xylene (DPX).[21]

The kidney and colonic tissues were dissected, washed and a 10% homogenate of the tissue made in chilled 1 mM tris-50 mM mannitol buffer (pH 7.4). For colon, the intestinal segment starting from the ligament of Triez was dissected and thoroughly flushed with the chilled buffer. The homogenate was centrifuged at 1,000 x g for 10 min at 4^0C. The pellet was discarded and the supernatant was used for various biochemical estimations.

Alkaline phosphatase activity was assayed according to the method of Bergmeyer[22] where p-nitrophenyl phosphate was used as the substrate which was hydrolyzed by the enzyme to yield p-nitrophenol at an alkaline pH. The yellow color of p-nitrophenol was measured at 410 nm.

The activity of the three disaccharidase enzymes, sucrase, lactase and maltase was determined by measuring the D-glucose liberated from the respective sugar substrate using a glucose oxidase-peroxidase (GOD-POD) enzymatic system.[23] Nitric oxide (NO) production by nitric oxide synthase was estimated by measuring the nitrite, a stable metabolic product of NO which quickly reacts with oxygen to yield nitrite. Nitrite thus formed, reacts with Griess reagent to form a purple azo dye, the color of which can be read at 540 nm.[24] The citrulline assay was based on its reaction with diacetyl-monooxime and the absorbance of the color produced was measured at 530 nm.

Results

The weight change profile showed a linear growth in the body weight during a complete six week treatment schedule which was shown in figure 1. No significant change in the body weight was observed between the control and the treated animals. Table I shows the total and the differential leukocyte counts in the different treatment groups during a six weeks treatment regimen. Eto-1 group showed an overall decrease in total leukocyte counts as well as the individual count of neutrophils, lymphocytes, monocytes and eosinophils in comparison to the control group. On the other hand, Eto-2 group showed a fairly significant increase in the leukocyte counts. The neutrophils did not show much change in the cell counts.

Table II demonstrated the activity of the four different enzymes in the kidney namely, alkaline phosphatase, sucrase, lactase and maltase which shows a highly significant decrease in both the Eto-1 and Eto-2 groups when compared to the controls. However, the alkaline phosphatase activity in colon showed a significant increase in both the treated groups (table III). Table IVdemonstrates that there was no significant change in the nitric oxide and citrulline level in kidney in the Eto-1 and Eto-2 groups of the animals as compared to the

Table II
Effect of etoricoxib on certain enzymes in the homogenate of kidney

Groups	*Enzyme assayed (μ moles/mg protein)*			
	Alkaline phosphatase	*Sucrase*	*Lactase*	*Maltase*
Control	0.588 ± 0.058	4.048 ± 0.136	5.408 ± 0.152	14.850 ± 0.683
Etoricoxib 1	0.399 ± 0.037***	2.504 ± 0.464***	3.28 ± 0.263***	6.877 ± 0.719***
Etoricoxib 2	0.523 ± 0.054*	2.156 ± 0.203***	3.294 ± 0.244***	7.718 ± 1.166***

Values are mean ± SD of six independent observations.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

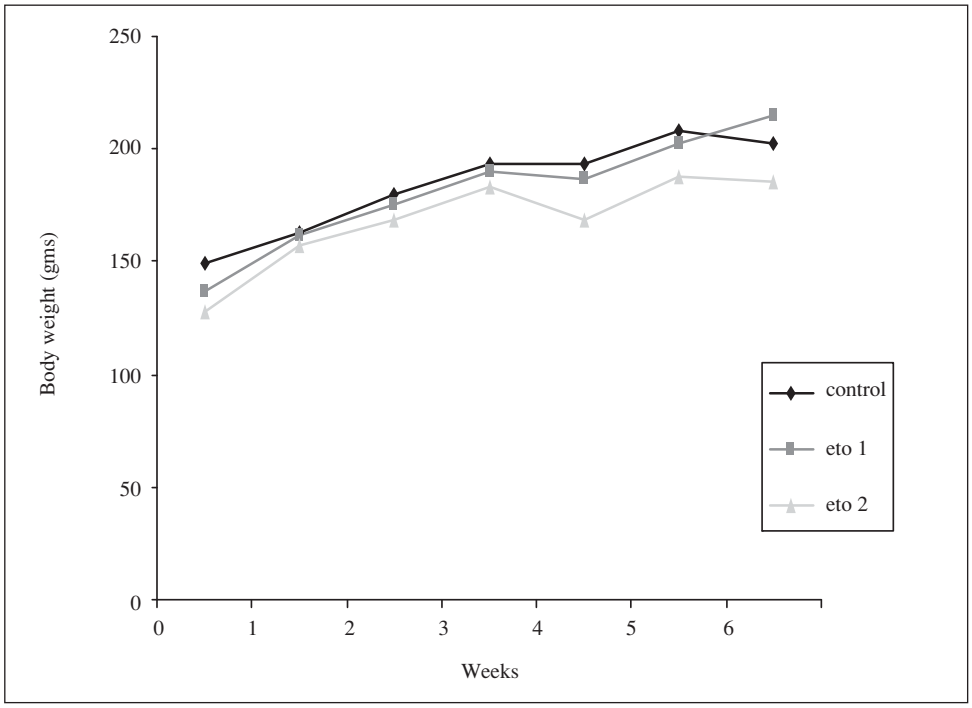

Fig. 1.—Effect of etoricoxib on animal body weight during a treatment of six weeks.

Table III
Effect of etoricoxib on alkaline phosphatase activity in colon

Groups	*Alkakine phosphatase activity (μ moles/mg protein)*
Control	0.424 ± 0.033
Etoricoxib 1	0.789 ± 0.099***
Etoricoxib 2	1.252 ± 0.130***

Values are mean ± SD of six independent observations.
*** $p < 0.001$.

controls while an increase was registered in the colonic tissues for the same in both the treatment groups.

Histologicaly, the paraffin embedded sections of colon and kidney were critically examined under light microscope following hematoxylin and eosin staining (H/E). The normal histological architecture of colon comprises of mucosal layer containing crypt lined with the various epithelial cells which included absorptive columnar cells, mucin producing goblet cells and neuroendocrine cells (fig. 2). These are embedded in the connective tissues called stroma. Mucosa rests over the sub mucosa below which lines the muscularis mucosa. The H/E results produced no major histoarchitectural changes in etoricoxib treated animals when compared with the control. Figure 3 shows the histoarchitecture of the kidney cortex. The Bowman's capsule structure was prominent. However, no major alteration was seen in both the etoricoxib groups in kidney, when compared to the controls (fig. with Eto-2 not shown). Figure 4 which shows the effect of Eto-1 treatment on the kidney histoarchitecture in the medullary region also revealed no major change in the same.

Table IV
Effect of etoricoxib on nitric oxide and citruline levels in kidney and colon

Groups	*Nitric oxide (nmoles/ml)*		*Citruline (nmoles/ml)*	
	Kidney	*Colon*	*Kidney*	*Colon*
Control	16.906 ± 3.162	14.117 ± 2.324	13.2 ± 0.098	1.77 ± 0.247
Etoricoxib 1	14.572 ± 1.259	17.187 ± 2.324***	13.0 ± 1.601	2.07 ± 0.947
Etoricoxib 2	16.241 ± 0.929	15.296 ± 3.052	14.7 ± 1.293	1.92 ± 0.230

Statistical analysis:
Values are mean ± SD of six independent observations.
*** $p < 0.001$.

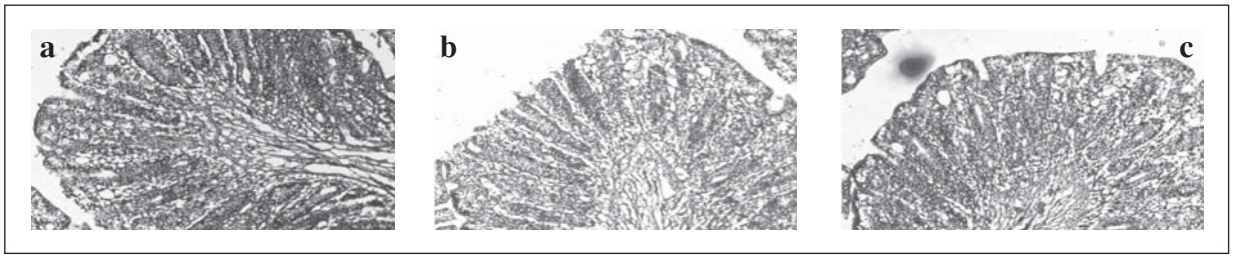

Fig. 2.—Photomicrograph showing the colonic mucosal surface of a) Control, b) Etoricoxib 1 and C) Etoricoxib 2 (400 X).

Discussion

NSAIDs are among the most widely prescribed class of pharmaceutical agents worldwide, having broad clinical utility in treating pain, fever and inflammation.[25,26] The anti-inflammatory action of NSAIDs rests in their ability to inhibit the activity of COX enzymes which in turn results in a diminished synthesis of proinflammatory prostaglandins (PGs).[27] COX-1 and COX-2, the two isoforms of COX are almost identical in structure but have important differences in substrate and inhibitor selectivity.[28] COX-1 synthesizes protective PGs which preserved the integrity of stomach and intestinal lining and maintain normal functioning of kidney as well. It also plays a role in the production of thromboxane A_2, causing an aggregation of platelets to prevent inappropriate bleeding.[29] On the other hand COX-2 emerged out as an inducible isoform for it could be induced by inflammatory stimulus and by cytokines in migratory and other cells.[30] The discovery of COX-2 isoenzyme and the characterization of its role in inflammation fostered the development of a new class of compounds that selectively inhibits COX-2 without affecting the COX-1 dependent PG biosynthesis necessary for physiological functions.[31] This new generation of anti-inflammatory drugs has been proven *in vitro* to selectively inhibit COX-2 activity and used to be as efficacious as the standard NSAIDs (both COX-1 and COX-2 inhibitors) in a number of *in vivo* models of inflammation (rat carrageenan-induced foot paw edema and rat adjuvant-induced arthritis)[32] and hyperalgesia (rat carrageenan-induced hyperalgesia).[33] Two selective COX-2 inhibitors in particular (called COXIBs) rofecoxib and celecoxib, have proven to provide significant relief in clinical trials of the signs and symptoms of osteoarthritis and rheumatoid arthritis and in eliminating pain following dental extraction, while reducing the incidence of gastrointestinal ulcers and erosions as seen with standard NSAID therapy.[34] Moreover, these eagerly awaited highly selective COX-2 inhibitors are of great interest because they may represent an alternative therapeutic option for the treatment of inflammation in diseases such as cirrhosis with ascites in which renal function is critically dependent on PGs.[35] However, in recent times unfortunately both rofecoxib and celecoxib have been reported to produce cardiovascular complications[36,37] and therefore necessitates searching for safer drugs. A second generation of selective COX-2 inhibitors such as valdecoxib, lumiracoxib and etoricoxib is currently under evaluation for clinical use,[38] and among these, etoricoxib has shown particular promise in chemoprevention in colon cancer in animal studies recently in our laboratory.[14-18]

The results of the present study wherein two different doses of etoricoxib were used in rats, one at the

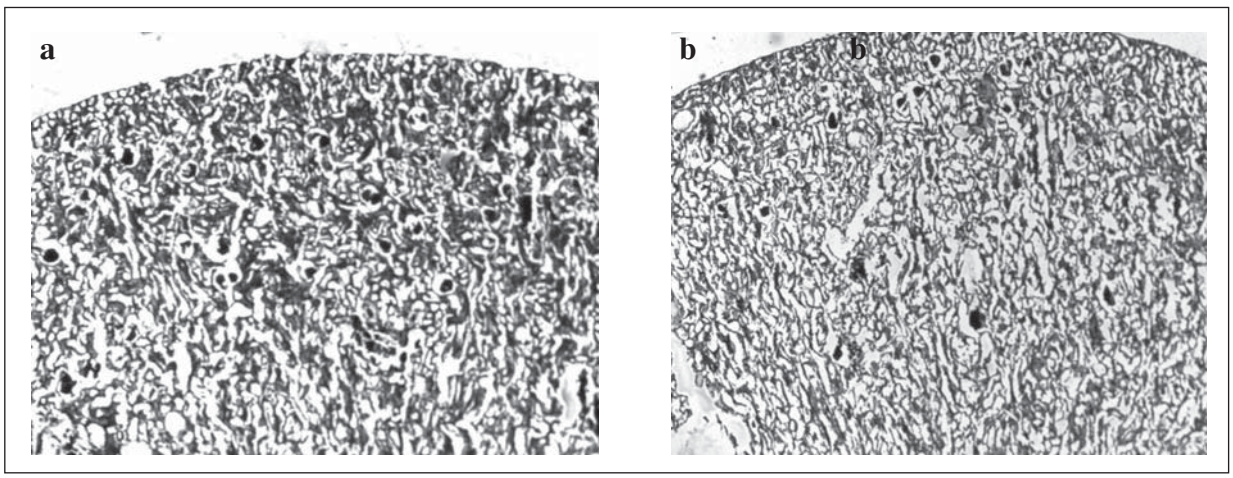

Fig. 3.—Photomicrograph showing the cortex region of a) Control and b) Etoricoxib 1 treated rat kidney cortex (100 X).

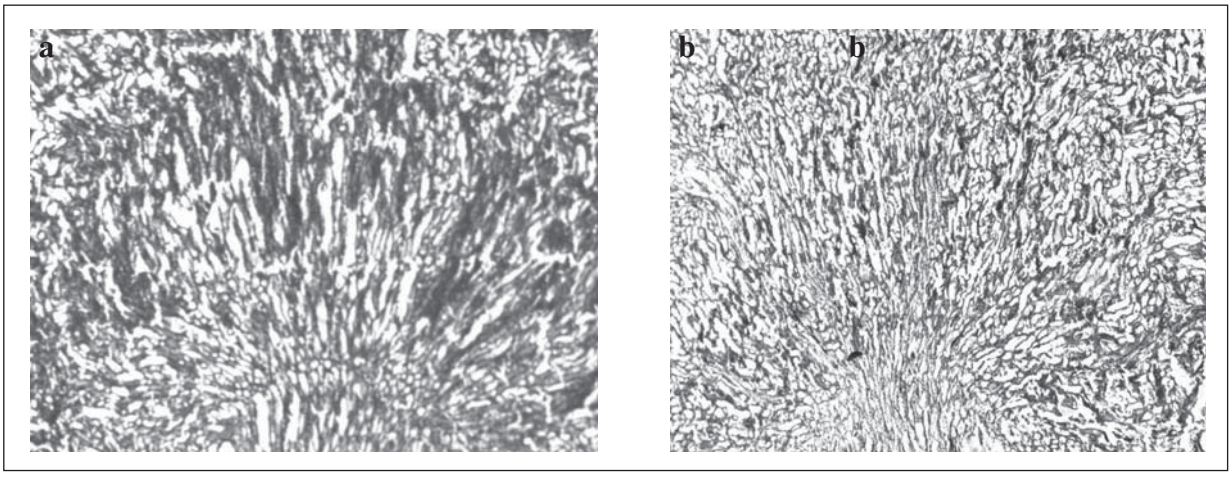

Fig. 4.—Photomicrograph showing the medulla region of a) Control and b) Etoricoxib 1 treated rat kidney medulla (100 X).

anti-inflammatory therapeutic dose and the other at ten times higher conclusively show that the drug does not interfere with the normal growth profile of the animal as well as the structural and functional parameters of kidney and colon. However, it was also demonstrated that etoricoxib at both the dose can influence the activities of sucrase, maltase, lactase and alkaline phosphatase in kidney. These enzyme activities are intimately associated with the process of membrane transport in the kidney brush border as shown by us earlier.[39] An increase in alkaline phosphatase activity in colon is seen in the present study where it has been reported to have a link with the transport of phosphate and calcium ions[40] may play a crucial role in signal transduction mechanism in the colonic brush border membrane.[41]

NO is produced by three nitric oxide synthase (NOs) enzymes. Endothelial NOs and neuronal NOs are both constitutively expressed while inducible NOs expression is enhanced by various inflammatory cytokines.[42] The role of NO in carcinogenesis is controversial as NO has both anti-tumor and tumor promotive properties.[43] The principal role of NO in the cellular microenvironment may depend on various factors such as the level of NO production and the genetic make up of the cells.[44] There are two pathways of citrulline production. It can be derived from arginine/NOs pathway and/or arginine/arginase pathway.[45] NOs pathway being responsible for the production of NO as well as citrulline, may play a major role in cell growth and proliferation. The present study of etoricoxib treatment at two different dose level led to no significant change in NO and citrulline level in the kidney tissues, while in colon only, NO was found to be increased and the citrulline level unaltered. Etoricoxib may help in replenishing the highly protective cells of colon as a little higher level of NO than normal is required for cell differentiation.[46] The results therefore suggest that etoricoxib may modulate the cellular environment in case of colon while no effects are seen in the kidney. Based on the present results it can be concluded that the specific COX-2 inhibitor, etoricoxib is a safe drug for therapeutic use at its ED50 value.

References

1. Vane JR, Bottling RM. The mechanism of action of aspirin. *Thromb Res* 2003; 110: 255-258.
2. Sengupta S, Lynda A, Sellers et al. Cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs inhibit hepatocyte growth factor/scatter factor-induced angiogenesis. *Cancer Res* 2003; 63: 8351-8359.
3. Gretzer B, Maricic N, Respondek M et al. Effects of specific inhibition of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the rat stomach with normal mucosa and after acid challenge. *Br J Pharmacol* 2001; 132: 1565-1573.
4. Vane JR, Bakhle YS, Botting RM. Cyclooxygenase 1 and 2. *Ann Rev Pharmacol Toxicol* 1998; 38: 97-120.
5. Willoughby DA, Moore AR, Colville-Nash PR. COX-1, COX-2 and COX-3 and the future treatment of chronic inflammatory disease. *Lancet* 2000; 355: 646-648.
6. Bombardier, Laine L, Reicin A. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New Engl J Med* 2000; 343: 1520-1528.
7. Schwartz JI, Chan, CC, Mukhopadhyay S. Cyclooxygenase-2 inhibition by rofecoxib reverses naturally occurring fever in humans. *Clin Pharmacol Ther* 1999; 65: 653-660.
8. Emery P, Zeidler H, Kvien TK et al. Celecoxib versus diclofenac in long- term management of rheumatoid arthritis: randomized double-blind comparison. *Lancet* 1999; 354: 2106-2111.
9. Matsumoto J, Melian A, Mandel DR. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. *J Rheumatol* 2002; 29: 1623-1630.
10. Riendeau D, Percival MD, Brideau C. Etoricoxib: a preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther* 2001; 296: 558-566.
11. Gregory LB, Michael HS, Jeffrey GM *et al*. Acute renal failure and hyperkalaemia associated with cyclooxygenase-2 inhibitors. *Nephrol Dial Transplant* 2004; 19: 1149-1153.
12. Harris RC. Cyclooxygenase-2 in the kidney. *J Am Soc Nephrol* 2000; 11: 2387-2394.
13. Oshima M, Taketo MM. COX inhibitor, suppression of polyposis, and chemoprevention. *Nippon Yakurigaku Zasshi* 2002; 120 (5): 276-84.
14. Kanwar SS, Vaiphei K, Nehru B et al. Chemopreventive effects of non steroidal anti-inflammatory drugs on 1, 2-dimethylhydrazine-induced colon carcinogenesis in rats. *Toxicol Mecha Meth* 2007; 17: 1-8.

15. Kanwar SS, Vaiphei K, Nehru B et al. Chemopreventive effects of non-steroidal anti-inflammatory drugs in the membrane lipid composition and fluidity parameters of the 1, 2-dimethylhydrazine induced colon carcinogenesis in rats. *Drug Chem Toxicol* 2007; 30: 293-30.
16. Kanwar SS, Vaiphei K, Nehru B et al. Antioxidative effects of Non-steroidal anti-inflammatory drugs (NSAIDs) during the initiation stages of experimental colon carcinogenesis in rats. *J Env Pathol Toxicol Oncol* 2008; 27 (2): 89-100.
17. Mittal N, Kanwar SS, Sanyal SN. The effect of etoricoxib, a cyclooxygenase-2 specific inhibitor on the 1, 2-dimethylhydrazine administered rat intestinal membrane structure and function. *Toxicol Mech Meth* 2007; 18: 53-62.
18. Mittal N, Kanwar SS, Sanyal SN. Effect of non-steroidal anti-inflammatory drugs and the pro-carcinogen 1, 2 dimethylhydrazine on the antioxidant defense system. *Int J Toxicol* 2007; 27: 169-174.
19. Dacie JV, Lewis K. Practical Haematology. 4th ed. Churchill, London 1968.
20. Pearse AGE. In: *Histochemistry, Theoritical and Applied*. 3rdEdn, p-660 Vol 1. Churchill, Livingstone, London 1968.
21. Humanson GL. In: *Basic procedures – Animal tissue technique, Part-1*, pp. 1961; 130-132.
22. Bergemeyer HU. Phosphatase (phosphomonoesterases). Determination in serum with p – nitrophenyl phosphate. In: Methods of Enzymatic Analysis, HU Bergmeyer (Ed), 1963, pp. 783-785. Academic Press, New York.
23. Dahlqvist A. Methods for assay of intestinal disaccharides. *Anal. Biochem* 1964; 7: 18-25.
24. Boyde TR, Rahmatullah M. Optimization of conditions for the colorimetric determination of citrulline, using diacetyl monoxime. *Anal Biochem* 1980; 107 (2): 424-31.
25. Flower RJ, Moncada S, Vane JR et al. Analgesic – antipyretics and anti inflammatory agents: drugs employed in treatment of gout. The Pharmacological Basis of Therapeutics: Macmillan. 1992; pp. 674.
26. Payan DG, Katzung BG. NSAID's: Non-opioid analgesics; drugs used in gout, in: Basic and Clinical Pharmacology; Katzung BG (Ed), 1995; pp. 536-559. Appleton and Lange, Norwalk.
27. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin- like drugs. *Nat New Biol* 1991; 231: 232-235.
28. Jouzeau JY, Terlain B, Abid A et al. Cyclo-oxygenase isoenzymes. How recent findings affect thinking about nonsteroidal anti-inflammatory drugs. *Drugs* 1997; 53 (4): 563-582.
29. Funk CD, Funk LB, Kennedy ME et al. Human platelet/erythroleukemia cell prostaglandin G/H synthase: cDNA cloning, expression, and gene chromosomal assignment. *FASEB J* 1991; 5: 2304-2312.
30. Raz A, Wyche A, Fagan D et al. The cell biology of fibroblast cyclooxygenase. *Adv Exp Med Biol* 1989; 259: 1-21.
31. Gilroy DW, Tomlinson A, Willoughby DA. Differential effects of inhibitors of cycloxygenase (cycloxygenase 1 and cycloxygenase 2) in acute inflammation. *Eur J Pharmacol* 1998; 355: 211-217.
32. Smith CJ, Zhang Y, Koboldt CM. Pharmacological analysis of cycloxygenase-1 in inflammation. *Proc Natl Acad Sci (USA)* 1998; 95: 13313-13318.
33. Warner TD, Giuliano F, Vojnovic I et al. Nonsteroid drug selectivities for cyclo-oxygenase 1 rather than cyclo-oxygenase 2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci (USA)* 1999; 967: 563-756.
34. Lanas A. Clinical experience with cyclooxygenase-2 inhibitors. *Rheumatol* 2002; (Supl. 1): 16-22.
35. López-Parra M, Claria J, Planaguma A et al. Cyclooxygenase-1 derived prostaglandins are involved in the maintenance of renal function in rats with cirrhosis and ascitses. *Brit J Pharm* 2002; 135: 891-900.
36. Aguilar JFN, Antich IA, Martinez AP et al. Cycloxygenase-2 inhibition in colon experimental carcinogenesis. *Rev Esp En En form Dig (Madrid)* 2005; 97: 637-647.
37. Subhashini J, Mahipal SVK, Reddana P. Anti-proliferation and apoptotic effects of celecoxib on human chronic myeloid leukemia in vitro. *Cancer Lett* 2005; 224: 31-43.
38. Esser R, Berry C, Du Z et al. Preclinical pharmacology of lumiracoxib: a novel selective inhibiter of cycloxygenase-2. *Br J Pharmacol* 2005; 144: 538-550.
39. Sanyal SN, Singh G, Kanwar SS. Thermotropic lipid phase transition and the behavior of hydrolytic enzymes in the cortex brush border membrane. *Chem Biodiver* 2006; 3: 1102-1115.
40. Shiffle H, Binswanger V. Calcium ATPase and intestinal calcium transport in uremic rats. *Am J Physiol* 1980; 238: G 424.
41. Lizumi Y, Hirano K, Sugoira M et al. Evidence for the physiological function of alkaline phasohatase. *Chem Pharm Bull* 1983; 32: 772-775.
42. Nathan C, Xie QW. Regulation of biosynthesis of nitric oxide. *J Biol Chem* 1994; 269: 13725-13728.
43. Ricciardolo FL, Sterk PJ, Gaston B. Nitric oxide in health and disease of the respiratory system. *Physiol Rev* 2004; 84: 731-765.
44. Wu G, Morris SM. Arginine metabolism: nitric oxide and beyond. *Biochem J* 1998; 336: 1-17.
45. Lala PK. Significance of nitric oxide in carcinogenesis, tumor progression and cancer therapy. *Cancer Metastasis Rev* 1998; 17: 1-6.
46. Stuehr DJ, Marletta MA. Synthesis of nitrite and nitrate in murine macrophage cell lines. *Cancer Res* 1987; 47 (21): 5590-5594.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):333-339
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Olive oil-diet improves the simvastatin effects with respect to sunflower oil-diet in men with increased cardiovascular risk. A preliminary study

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Abstract

Background and aims: **Concomitant intake of statins together with certain foods may affect their therapeutic effects. The purpose of this preliminary study was to determine the modulating effect of two culinary oils on the hypolipemic effect of statins. Subject and Methods: Twenty-five men with severe hypercholesterolemia and high estimate cardiovascular risk (> 20% according to the Adult Treatment Panel III of USA National Institutes of Health, ATP-III) were enrolled in an observational follow-up study to test lipoprotein profile changes after six month 20-mg/d Simvastatin treatment. Thirteen volunteers using sunflower oil as the habitual culinary fat, and 12 using olive oil, were selected by non-probabilistic incidental sampling. Volunteers consent in follow their habitual diets and to maintain diet characteristics throughout the study. Diet was evaluated through the study by three 24-h recalls and a food frequency questionnaire.**

Results: **The energy contribution of fat (P = 0.019) and MUFA (P < 0.001) was higher in the olive oil-group while that of PUFA (P = 0.001) and alcohol (P = 0.005) was higher in the sunflower oil-group. TC/HDL-cholesterol and the ATP-III 10-year risk percent decreased more (P < 0.05) in the olive oil group. TC and the TC/HDL-cholesterol and the LDL-cholesterol/HDL-cholesterol ratios and the ATP-III 10-year risk percent decreased significantly more (P < 0.05) in the olive oil-group after BMI, energy and alcohol intakes were adjusted.**

Conclusion: **Data suggest that although Simvastatin is a very effective hypolipemic drug, olive oil-diets in preference to sunflower oil-diets must be consumed in patients with high cardiovascular risk.**

(*Nutr Hosp*. 2009;24:333-339)

Key words: *Simvastatin. Olive oil. Sunflower oil. Cholesterol. Lipoprotein-cholesterol. Cardiovascular risk. Drug-food interaction.*

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Recibido: 11-II-2009.
Aceptado: 13-II-2009.

LAS DIETAS CONTENIENDO ACEITE DE OLIVA MEJORAN LOS EFECTOS DE SIMVASTATINA RESPECTO A DIETAS CON ACEITE DE GIRASOL EN HOMBRES CON RIESGO CARDIOVASCULAR ELEVADO. ESTUDIO PRELIMINAR

Resumen

Introducción y objetivos: **La ingesta de algunos alimentos junto con estatinas puede afectar los efectos terapéuticos del fármaco. Este estudio preliminar pretende determinar el efecto modulador de dos tipos de aceites culinarios sobre los efectos hipolipemiantes de las estatinas.**

Métodos: **Mediante muestreo no probabilístico, 25 hombres con hipercolesterolemia severa y alto riesgo cardiovascular (> 20% según el Panel III para tratamiento de adultos de los Institutos de Salud USA, ATP-III) participaron en el estudio observacional para ver los cambios en el perfil lipoproteico después de seis meses de tratamiento con 20 mg/día de Simvastatina. 13 voluntarios consumían habitualmente aceite de girasol como principal grasa culinaria y 12 aceite de oliva. Todos los sujetos consintieron en mantener sus hábitos alimentarios durante el estudio. Para evaluar la dieta se usaron 3 recuerdos de 24 horas y una frecuencia de consumo.**

Resultados: **El aporte calórico de la grasa (P = 0,019) y de los AGM (P < 0,001) fue mayor en el grupo que consumía aceite de oliva, mientras que el de AGP (P = 0,001) y alcohol (P = 0,005) fue menor. El cociente colesterol/HDL-colesterol y el riesgo cardiovascular disminuyeron más (P<0.05) en los pacientes consumiendo aceite de oliva. Después de ajustar para IMC y para ingesta calórica y de alcohol, el colesterol total y los ratios colesterol/HDL-colesterol y LDL-colesterol/HDL-colesterol y el riesgo cardiovascular ATP-III disminuyeron significativamente más (P < 0,05) en el grupo de aceite de oliva.**

Conclusiones: **Los resultados sugieren que aunque Simvastatina es un fármaco hipolipemiante muy efectivo, la inclusión de aceite de oliva, frente a aceite de girasol, mejora dicho efecto en pacientes con alto riesgo cardiovascular.**

(*Nutr Hosp*. 2009;24:333-339)

Palabras clave: *Simvastatina. Aceite de oliva. Aceite de girasol. Colesterol. Lipoprotein-colesterol. Riesgo cardiovascular. Interacción fármaco-nutriente.*

Introduction

Statins are drugs that inhibit the rate-limiting enzyme of cholesterol synthesis 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (3-OH-3-MGCoA).[1,2] The reduction in intracellular cholesterol levels stimulates synthesis of low density lipoprotein (LDL) receptors and their expression on the surface of liver cells. These receptors are responsible for the uptake of LDL in addition to that of their precursors, very low density lipoprotein (VLDL) and VLDL remnants. This effect of statins on VLDL also explains their capacity to reduce triglyceride levels, although to a lesser degree and in a less consistent manner.[1,2] Thus, at present, statins are extendedly prescribed in patients with different types of dyslipemia.[1,2] The statins presently available are mainly eliminated by the liver. Simvastatin, lovastatin and atorvastatin are metabolised by cytochrome P-450 3 A4 (CYP 3 A4), while fluvastatin is metabolised by CYP 2 C9. Only small amounts of pravastatin, rosuvastatin and pitavastatin are metabolised by this way.[3,4] PUFA have been shown to activate P-450 cytochrome activity, while SFA exert lower cytochrome activation with MUFA exerting intermedium effect.[5] Concomitant intake of statins together with certain foods may produce alterations in their pharmacokinetics or pharmacodynamics resulting in higher risk of adverse reactions in some cases or lower pharmacological action in others.[1,3,4]

Very little information exists on the possible relation between unsaturated oil intake and statin effects.[6] This is surprising because culinary oils contribute more than 50% of the consumed fat in some countries.[7] In Spain, due to economic reasons, olive oil consumption has been partially replaced by other cheaper oils, such us sunflower. This partial substitution, together with other profound food habits changes (e.g. low oily fish and high lean fish consumptions), have contributed to the increase of omega-6 fatty acid and the omega-6/omega-3 ratio observed through the last few decades in Spain.[8]

Dietary fatty acids have profound effect on lipid and lipoprotein levels.[9-14] Mattson & Grundy[10] found that oleic acid lowered plasma cholesterol as much as linoleic acid did. However, it is more generally accepted that n-6 PUFA (e.g. linoleic acid) produces a more prominent hypocholesterolemic effect than MUFA (e.g. oleic acid) do.[13,14]

Taking into account all that we previously commented on, we hypothesized that the culinary oil ingestion, due to its specific composition, can modulate the hypolipemic effect of statins. Moreover, this effect can be also changed due to the effect of PUFA on CYT 450.[3,4] Thus, the main goal of this preliminary study was to test how the diet composition (mainly by the mean of the culinary oil used) influences the hypolipemic effect of statins in men with increased cardiovascular risk. Moreover, the effect of the basal total cholesterol (TC), LDL-cholesterol, and triglyceride levels on this diet-drug interaction was also tested.

Methods

Sample and study design

In a pharmacy office located in the industrial Area close to Aviles, Asturias (Spain), subjects just diagnosed of hypercholesterolemia and going to start treatment with Simvastatin were asked to participate in an observational follow-up study. A non-probabilistic incidental sampling was selected to test the influence of oil type in the hypolipemic effects of Simvastatin.

Volunteers had to fulfil the following eligibility criteria: a) gender: men; b) age: 45-65 years b) BMI ≥ 20-35 kg/m^2; c) diagnosed of hypercholesterolemia (Serum total cholesterol ≥ 250 mg/dL or ≥ 6.46 mmol/L, LDL-cholesterol ≥ 160 mg/dL or 4.14 mmol/L); d) to have at least one extra cardiovascular risk (e.g. hypertension) or familiar antecedents of cardiovascular accident; e) going to start with statin treatment as hypocholesterolemic drug; g) to maintain the doses and type of statins through the treatment. Exclusion criteria: a) previous cardiovascular attack; a) type I diabetes; c) previously treated with statins.

Forty volunteers fulfilling the previous criteria were selected among a total of 54 candidates. Although many subjects were conscious of using only olive oil or sunflower oil, ten of them were not finally selected because they did not show regular dietary habits. Informed consent was obtained from a total of 30 male participants. Twenty five of them were ready to receive Simvastatin while three of them Fluvastatin and the other two Atorvastatin. Thus, finally only volunteers on 20 mg/d Simvastatin were studied. The percentage change from baseline for TC concentration and the LDL-cholesterol/HDL-cholesterol ratio was determined a priori to be the primary outcome variables. Sample size was considered adequate taking into account previous studies on the influence of diet on lipid and lipoprotein concentrations.[15] Nonetheless, this study was designed to have a power of 85% (alpha 0.05) to detect a 20% difference between olive oil and sunflower groups in TC response. A pooled standard deviation of 10% for the change from baseline TC or LDL-cholesterol/HDL-cholesterol was assumed for this calculation.

The study was performed according to the guidelines of the Helsinki Declaration. Patients were of low to medium-low socioeconomic status and had low academic and professional qualifications. Subjects were questioned about the use of fibres or other drugs. Subjects were instructed to continue in their usual diets and oil used and to inform about any change in the diet and/or the hypocholesterolemic treatment. Patients were recruited six months later in the same place for a second blood draws.

Baseline anthropometric measurements were done by trained personnel using standard methods and calibrated equipment[16] at the previous cited phar-

macy office. The body height was measured with subjects standing barefoot and upright with the head in the Frankfort plane. Weight was measured on a Precision Health scale with the subjects wearing only their underclothes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Body weight changes (gains or losses) were refereed by volunteers at the end of the study. Volunteers were also asked about physical activity during the follow-up study. Blood systolic and diastolic pressures were measured following OMS recommendation using a Hg sphygmomanometer.[17]

Lipids and lipoprotein analysis

Blood was drawn in fasting conditions. Serum was obtained by blood centrifugation at 2,500 g during 30 min at room temperature. The lipid and lipoprotein analyses were performed about one week before starting the Simvastatin treatment and six months later. Routine enzymatic colorimetric measurements for TC and TAG were performed using kits and instructions of Boehringer, Mannheim, Germany). HDL-cholesterol was tested after VLDL and LDL precipitation with fosfotungstic acid and $MgCl_2$.[18] In no case were serum TAG higher than 360 mg/dL (4.04 mmol/L); thus, the Friedewald et al. formula[19] was used to calculate VLDL-cholesterol and LDL-cholesterol levels. All determinations were performed under quality control.

Cardiovascular risk

The cardiovascular risk was calculated using the Adult Treatment Panel III of USA National Institutes of Health (ATP-III) tables.[20]

Dietary survey

Information about habitual food intake was obtained at the pharmacy office using three 24h recall surveys throughout the study in non consecutive days and a validated six month food frequency questionnaire (Departamento de Nutrición, Facultad de Farmacia, Universidad Complutense de Madrid, Spain) by trained personnel. In most cases, the diet information obtained was checked with the wife's help. The portion size consumed was defined according a manual containing 147 set of pictures of simple foods and complex culinary dishes, and also recipe sizes.[21] Detailed information about the type and amount of oil consumed was obtained taking into account possible losses due to frying and other culinary processes. After assessing average food consumption, information about energy, protein, lipid, carbohydrates, fibre, cholesterol, saturated, monounsaturated and polyunsaturated fatty acid intakes were estimated using the food composition tables compiled in the DIETECA databank.[22]

Statistic study

Distribution normality was checked by Kolmogorov-Smirnov tests. TAG were normalized by using natural log. The possible interaction between the oil type and Simvastatin was checked by repeated measure test. Differences in treatment between basal values and at six months were tested by the Paired Student *t* test. Also, the possible effect of basal TC, LDL-cholesterol and TAG levels and the TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios were tested. Due to the influence of BMI, energy and alcohol consumption, data were also tested after including these variables as covariates in the statistical models. The SPSS version 15.0 was employed.

Results

Participants from both oil groups did not show significant differences in age, anthropometric characteristics, and physical activity (table I). No significant changes in physical activity and body weight were refereed by volunteers through the study. The consumption of tobacco tended to be higher among sunflower consumers (P = 0.066).

The mean values for energy, macronutrients, cholesterol and fibre intakes of the participants are shown in table II. The sunflower oil-group consumed more absolute amounts of alcohol (P = 0.003) and PUFA (P = 0.005) and lower of MUFA (P < 0.001). The energy contribution of MUFA was lower (P = 0.001) in the sunflower oil-group while that of alcohol (P = 0.002) and PUFA was higher (P = 0.011). Total lipid energy contribution tended to be lower in the sunflower oil-group (P = 0.066).

Table I
Baseline body mass index, physical activity and blood pressure of volunteers consuming an olive oil – or sunflower oil-diet

	Olive oil-group	*Sunflower oil-group*	*p*
Volunteers number	*n = 12*	*n = 13*	
Age (yr)	56.8 ± 4.2	56.6 ± 4.4	NS
BMI (kg/m^2)	28.7 ± 2.5	28.5 ± 1.6	NS
Physical activity*	0.8 ± 0.8	0.8 ± 0.7	NS
Cigarrete consumption (nr)	5.0 ± 9.0	12.3 ± 9.9	0.066

Data are mean ± SD. *Mean from 0: non active; 1: active; 2: very active; NS: Not significant.

Table II
Energy, macronutrients, fibre, cholesterol intakes and contribution of macronutrients to the total energy consumed by the volunteers consuming an olive oil – or sunflower oil-diet

	Olive oil-group	*Sunflower oil-group*	*p*
Volunteers number	*n = 12*	*n = 13*	
Energy (MJ)	14.3 ± 1.8	14.3 ± 1.8	NS
Protein (g)	128.3 ± 26.1	130.0 ± 37.7	NS
Lipids (g)	137.6 ± 4.2	130.7 ± 34.7	NS
Carbohydrates (g)	382.8 ± 8.9	384.8 ± 72.2	NS
Fibre (g)	29.3 ± 13.9	26.2 ± 9.0	NS
Alcohol (g)	20.3 ± 24.6	56.0 ± 29.2	0.003
SFA (g)	32.5 ± 9.8	34.9 ± 9.3	NS
MUFA (g)	65.3 ± 13.6	41.3 ± 12.4	< 0.001
PUFA (g)	26.4 ± 11.1	40.5 ± 11.4	0.005
Cholesterol (mg)	380.0 ± 151.0	405.0 ± 247.1	NS
Energy contribution			
Protein (% kcal)	15.4 ± 2.9	14.5 ± 2.5	NS
Lipids (% kcal)	37.1 ± 4.9	33.1 ± 5.5	0.066
Carbohydrates (% kcal)	43.4 ± 6.5	41.3 ± 6.9	NS
Alcohol (% kcal)	4.1 ± 4.8	11.1 ± 5.4	0.002
SFA (% kcal)	8.7 ± 2.2	8.9 ± 1.9	NS
MUFA (% kcal)	17.6 ± 2.9	10.5 ± 2.6	0.001
PUFA (% kcal)	7.2 ± 3.2	10.2 ± 1.8	0.011

Data are mean ± SD. NS: Not significant.

Table III shows the effect of Simvastatin after six months treatment in both oil-groups. This statin, without considering the culinary oil consumed, significantly reduced ($P < 0.001$) serum lipid and lipoprotein levels (except HDL-cholesterol) after 6 months of treatment. No significant differences on TC, LDL-cholesterol, HDL-cholesterol and TAG concentrations, systolic and diastolic pressures, and absolute risk were found at the baseline between the two oil-groups. At six months treatment, LDL-cholesterol, the TC/HDL-cholesterol ratio and the ATP-III 10-year risk percent tended to be lower ($P = 0.067$, $P = 0.082$, and $P = 0.064$, respectively) in the olive oil-group. The TC/HDL-cholesterol ratio, the absolute risk punctuation and the 10-year risk percent decreased significantly more during the six months treatment in the olive oil-group ($P = 0.05$). When data were adjusted for the BMI and alcohol and energy consumptions, the decreases in cholesterol, and in the TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios were also significantly higher in the olive oil-group than in the sunflower oil-one ($P < 0.05$).

Discussion

This study shows the benefits of the Simvastatin therapy in volunteers with ATP-III risk higher than 20%. Diet of volunteers, especially that of those consuming olive oil, corresponds in general terms to the nowadays diet followed in Spain.[8] This diet is far from the nutritional guidelines[23] where carbohydrates should contribute more than 50% of total energy, lipids 30-35%, proteins 10-15% and alcohol < 10%. In terms of fat energy contribution, the olive oil-group seems to follow a less adequate diet. Some time ago, Keys et al.[24] found that the energy contribution of fat highly influenced serum cholesterol levels in men aged 40-49. However, Keys et al.[11] in the Seven Countries Study also found that cardiovascular mortality was reduced in people consuming high amount of MUFA as oleic acid. Energy consumption was high but in line with energy expenditure because body weight and BMI did not significantly change during the six months study. Volunteers on sunflower oil-group tended to consume more tobacco and alcohol. Other studies have reported similar findings. There is now consistent evidence that dietary patterns are related to other behaviours such as smoking.[25]

In accordance with other studies,[1,2] data of the study clearly show, with independence of the diet followed, the benefits of Simvastatin consumption in the lipid, blood pressure profile of patients with high cardiovascular risk. In fact, in both dietary groups TC and LDL-cholesterol decrease at least 17% and 19%, respectively.

Although the low number of participating volunteers appears as the main limitation of this preliminary study, as previously commented, this study was designed to have a power of 85% (alpha 0.05) to detect a 20% difference between olive oil and sunflower groups in TC response. When results obtained were related to the oil consumed very interesting data were obtained. Baseline TC, TAG, LDL-cholesterol and HDL-cholesterol levels and the TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol risk ratios were very similar in both groups. Moreover, age, and educational and sociological status were also similar. In both dietary groups, Simvastatin produced significant variations in all parameters studied, except HDL-cholesterol. The absolute and percentage changes differ in both oil-groups for the TC/HDL-cholesterol and the ATP-III cardiovascular risk, suggesting that the effect of Simvastatin on this risk ratio was different in diets differing about 5% in energy but presenting a different fatty acid profile. Alcohol consumption is known to affect HDL-cholesterol[26] while overweight/obese people present high TC and low HDL-cholesterol levels;[27] thus, adjusting data BMI and for energy and alcohol consumptions gives a more reliable information of differences between oils in the present study. Adjusting alcohol consumption is also important, because in a prospective, double-blind crossed study involving

Table III
Lipid and lipoprotein changes after simvastatin treatment in volunteers consuming an olive oil – or sunflower oil-diet

	Olive oil group	*Sunflower oil-group*	*Absolute change in olive oil-diet vs Sunflower oil-diet (p)*
Volunteers number	*n = 12*	*n = 13*	
Baseline TAG (mmol/L)	2.22 ± 0.60	1.83 ± 0.75	
Final TAG (mmol/L)	1.61 ± 0.73	1.34 ± 0.58	
Change respect to baseline (%)	28.7 ± 17.2[a]	23.6 ± 16.4[a]	NS
Baseline cholesterol (mmol/L)	8.01 ± 1.01	8.05 ± 1.01	
Final cholesterol (mmol/L)	6.16 ± 0.64	6.62 ± 0.80	
Change respect to baseline (%)	22.5 ± 9.4[a]	17.5 ± 7.6[a]	NS (0.04)
Basal LDL-cholesterol (mmol/L)	5.99 ± 1.04	6.15 ± 1.06	
Final LDL-cholesterol (mmol/L)	4.42 ± 0.66	5.00 ± 0.90‡	
Change respect to baseline (%)	25.1 ± 11.8[a]	19.1 ± 10.0[a]	NS (0.06)
Basal HDL-cholesterol (mmol/L)	1.00 ± 0.10	1.01 ± 0.10	
Final HDL-cholesterol (mmol/L)	1.00 ± 0.07	1.00 ± 0.07	
Change respect to baseline (%)	-0.2 ± 6.2	1.0 ± 5.3	NS
Basal TC/HDL-cholesterol	8.05 ± 1.13	8.01 ± 1.13	
Final TC/HDL-cholesterol	6.18 ± 0.83	6.68 ± 1.08‡	
Change respect to baseline (%)	22.5 ± 8.0[a]	16.5 ± 4.5[a]	0.05 (0.036)
Basal LDL-cholesterol/HDL-cholesterol	6.03 ± 1.31	6.16 ± 1.10	
Final LDL-cholesterol/HDL-cholesterol	4.45 ± 0.83	5.04 ± 1.09	
Change respect to baseline (%)	19.0 ± 9.0[a]	13.0 ± 7.1[a]	NS (0.041)
Basal Systolic pressure	155.8 ± 20.7	165.4 ± 25.7	
Final Systolic pressure	155.2 ± 16.6	159.0 ± 21.8	
Change respect to baseline	2.7 ± 3.9[a]	3.6 ± 3.7[a]	NS
Basal Diastolic pressure	92.5 ± 17.1	100.8 ± 18.9	
Final Diastolic pressure	90.2 ± 14.4	97.4 ± 16.0	
Change respect to baseline	2.1 ± 3.5[a]	2.9 ± 3.6[a]	NS
Basal Risk points	16.7 ± 1.6	17.5 ± 2.1	
Final Risk points	15.2 ± 1.6	16.7 ± 2.2	
Change respect to baseline	9.0 ± 3.9[a]	4.4 ± 5.2[a]	0.035 (0.03)
Basal 10-year risk percent	25.8 ± 4.2	26.5 ± 4.3‡	
Final 10-year risk percent	20.5 ± 14.9	25.2 ± 6.3‡	
Change respect to baseline	21.6 ± 14.9[a]	6.2 ± 12.6[b]	0.006 (0.04)

Data are mean ± SD. [a]$P < 0.001$; [b]$P < 0.01$ change respect to baseline; ‡p < 0.1 with respect to olive oil group. NS: Not significant. In parenthesis after BMI and energy and alcohol intakes adjustments.

patients with primary hypercholesterolemia receiving Fluvastatin for 6 weeks[28] it was found that 20 g of alcohol, diluted to 20% with lemonade modifies the metabolism of the drug; although no significant differences in the hypolipemic effect of Fluvastatin were found in that study. After adjusting data for BMI and for energy and alcohol consumptions a higher hypolipemic response and a higher cardiovascular protection to Simvastatin in olive oil group was found. Present results are relevant taking into account the importance of TC and the predictive power of TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios of future cardiovascular risk.[29]

At present no clear explanation for the present results can be drawn taking into consideration the theoretical higher hypocholesterolemic effect of linoleic acid than that of the oleic acid.[13,14] However, the dietary exchange of an olive oil and sunflower oil blend for extra virgin olive oil decreased the estimate cardiovascular risk and LDL in postmenopausal women.[15] MUFA and PUFA decrease LDL levels by increasing the cholesterol ester pool size, stimulating the mRNA genesis of the LDL receptor (LDL-R).[30] This regulatory effect increases when dietary cholesterol is high.[31] It has demonstrated that oleic acid stimulates LDL-R activity twice as much as linoleic acid does in hams-

ters.[31] Patients on MUFA diets tend to display a greater lymphocyte LDL-R activity than those of on PUFA diets.[32] Nonetheless, other explanations could be formulated. PUFA have been shown to activate P-450 cytochrome activity, while SFA exert lower cytochrome activation with MUFA causing intermedium effect.[5] Thus, we hypothesized that the half-life of Simvastatin is reduced due to a cytochrome-activating effect when the drug is consumed by patients following a sunflower oil-rich diet with respect to the same diet prepared with olive oil. Nonetheless, the possible increasing effect of olive oil polyphenols on Simvastatin pharmakocynetic, due to an inhibition of P-450 cytochrome,[33] should not be ruled out.

The benefits of Simvastatin suggested in the HDL-cholesterol[1,2] were not found in the present study. This fact can be partially explained by the already high levels of HDL-cholesterol found in these volunteers, because only 2 of the 25 volunteers studied showed baseline HDL-cholesterol levels < 35 mg/dL (< 0.90 mmol/L). Moreover, in the olive oil-group the higher intake of fat and olive oil could explain these relatively high HDL-cholesterol figures,[13,15] while in the sunflower oil-group the alcohol consumption would be involved in such high HDL-cholesterol levels[34] counterbalanced by the high levels of PUFA consumed.[10]

Conclusions

To summarize, Simvastatin consumed in the framework of an olive oil-diet produced higher decrease in the TC/HDL-cholesterol ratio that Simvastatin consumed together a sunflower oil-one. The effect was also significantly higher for the variation of TC, the TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios when data were adjusted for BMI, energy and alcohol consumptions. Olive oil-diets in preference to sunflower oil-diets must be consumed in hypercholesterolemic subjects treated with Simvastatin. Future work should be addressed to ascertain the possible role of different culinary oils and that of minor compounds (e.g. polyphenols, sterols) in this food-statin interaction.

Acknowledgements

Authors are indebted to physician and technical members of the Servicio de Salud de Avilés, Asturias (Spain) for their valuable collaboration in the study. The study was partially granted by Projects AGL 2005-07204-C02-01 and AGL-2008-04892-C03-02 .

References

1. Andrés S de, Lucena A, Juana P de. Interacciones entre los alimentos y las estatinas. *Nutr Hosp* 2004;19: 195-201.
2. Florez J, Freijanes J. Fármacos hipolipoproteinemiantes. Control de la obesidad. In: Florez J, Armijo JA, Mediavilla A, eds. Farmacología humana. Masson SA, pp. 950-953, Barcelona, 1997.
3. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. *Pharmacol Ther* 2006; 112: 71-105.
4. Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. Review. *Clin Pharmacokinet* 1997; 32: 403-425.
5. Sung M, Kim I, Park M, Whang Y, Lee M. Differential effects of dietary fatty acids on the regulation of CYP2E1 and protein kinase C in human hepatoma HepG2 cells. *J Med Food* 2004; 7: 197-203.
6. Gutiérrez-García MO. Estudio piloto. Interacción dieta-estatinas en una muestra poblacional dislipémica. Diploma de Estudios Avanzados. Facultad de Farmacia. Madrid: Universidad Complutense de Madrid, Spain, 2003.
7. Sánchez-Muniz FJ, Bastida S, Márquez-Ruiz G, Dobarganes MC. Effect of heating and frying on oil and food fatty acids. In: Fatty Acids in Foods and Their Health Implications, third edition, CK Chow, ed. CRC Press Taylor & Francis Group, pp. 511-543, Boca Raton, FL, 2007.
8. Serra L, Aranceta J (editors) Alimentación infantil y juvenil. Estudio enKid, Masson. Vol 3, pp. 83-178, Barcelona, 2002.
9. Keys A. Coronary heart disease global picture. *Atherosclerosis* 1975; 22: 149-192.
10. Mattson FH, Grundy SM. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res* 1985; 26: 194-202.
11. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R et al. The diet and 15 years death rate in the seven countries. *Am J Epidemiol* 1986; 124: 903-915.
12. Montoya MT, Porres A, Serrano S, Fruchart JC, Mata P, Gerique JAG, Castro GR. Fatty acid saturation of the diet and plasma lipid concentrations, lipoprotein particle concentrations, and cholesterol efflux capacity. *Am J Clin Nutr* 2002; 75: 484-491.
13. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb* 1992; 12: 911-919.
14. Kris-Etherton PM, Yu S. Individual fatty acid effects on plasma lipids and lipoproteins: human studies. *Am J Clin Nutr* 1997; 65 (5 Supl.): 1628S-44S.
15. Rodenas S, Rodríguez-Gil S, Merinero MC, Sánchez-Muniz FJ. Dietary exchange of an olive oil and sunflower oil blend for extra virgin olive oil decreases the estimate cardiovascular risk and LDL and apolipoprotein AII concentrations in postmenopausal women. *J Am Coll Nutr* 2005; 24: 361-366.
16. OMS. FAO-Unicef-WHO. Methodology of nutritional surveillance. Technical Report Series 53, WHO, Ginebra, 1976.
17. World Health Organization-International Society of Hypertension. Guidelines for the Management of Hypertension. Guidelines Subcommittee. 2003. http://www.who.int/cardiovascular_diseases/guidelines/hypertension_guidelines.pdf [consulted on 22-June-2006].
18. Finley PR, Schifman RB, Williams J, Lichtil DD. Use of Mg^{2+} dextran sulphate in its enzymatic measurements. *Clin Chem* 1978; 24: 931-933.
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein-cholesterol in plasma without use of preparative ultracentrifugation. *Clin Chem* 1972; 18: 499-502.
20. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in adults (Adults, Treatment Panel III) Executive Summary, Publication No 3670, National Heart, Lung, and Blood Institute. National Institutes of Health (NIH), Bethesda, 2001.
21. Mataix Verdú J, Llopis González J. Manual Gráfico e Contenido Nutricional de Pratos Galegos. JF Jiménez Contreras, RM Lendoiro Otero and MJ Meniño Olivera, eds. Consellería de Sanidade, Carrefour, Galicia, 1993.

22. Moreiras O, Carbajal A, Cabrera L, Cuadrado C (eds.). Tablas de composición de alimentos. Ediciones Pirámide, Madrid, Spain, 2006.
23. Aranceta J. Objetivos Nutricionales y Guías Dietéticas. In: Nutrición y dietética, MT García-Arias and MC García-Fernández, eds. Secretariado de Publicaciones y Medios Audiovisuales Universidad de León, pp. 45-52, León, Spain, 2003.
24. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. *Lancet* 1957; 273: 959-966.
25. Villegas R, Salim A, Collins MM, Flynn A, Perry IJ. Dietary patterns in middle-aged Irish men and women defined by cluster analysis. *Public Health Nutr* 2004; 7: 1017-1024.
26. Hoenig MR, Kostner KM, Read SJ, Walker PJ, Atherton JJ. Implications of the obesity epidemic for statin therapy: shifting cholesterol metabolism to a high synthesis and low dietary absorption state. *Endocr Metab Immune Disord Drug Targets* 2007; 7: 153-166.
27. Bau PF, Bau CH, Rosito GA, Manfroi WC, Fuchs FD. Alcohol consumption, cardiovascular health, and endothelial function markers. *Alcohol* 2007; 41: 479-488.
28. Smit JW, Wijnne HJ, Schobben F, Sitsen A, De Bruin TW, Erkelens W. Effects of alcohol and fluvastatin on lipid metabolism and hepatic function. *Ann Int Med* 1995; 122: 678-680.
29. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 2007; 298: 776-785.
30. Daumerie CM, Woollett LA, Dietschy JM. Fatty acids regulate hepatic low density lipoprotein receptor activity through redistribution of intracellular cholesterol pools. *Proc Natl Acad Sci USA* 1992; 89: 10797-10801.
31. Dietschy JM. Dietary fatty acids and the regulation of plasma low density lipoprotein cholesterol concentrations. *J Nutr* 1998; 128: 444S-448S.
32. Garrido JA, Mata P. Tratamiento dietético de las dislipemias. In: Metabolismo lipídico. Investigación en Biomedicina, M de Oya, editor. Madrid: I.M. & C. 1994, pp. 253-270.
33. Stupans I, Stretch G, Hayball P. Olive oil phenols inhibit human hepatic microsomal activity. *J Nutr* 2000; 130: 2367-2370.
34. Hines LM, Stampfer MJ, Ma J, Gaziano JM, Ridker PM, Hankinson SE, Sacks F, Rimm EB, Hunter DJ. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med* 2001; 344: 549-555.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):340-346
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Influencia del zinc administrado a pacientes críticos con nutrición parenteral sobre los niveles de zinc plasmático, proteína C reactiva, interleuquina-6 y receptor soluble de interleuquina-6

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Resumen

Objetivos: **Estudiar, en pacientes críticos, la respuesta de los niveles de Zn en plasma (ZnPl), de IL-6 sérica, del IL-6sR y de la PCR en relación al Zn administrado en la NPT, para evitar la deficiencia o el exceso de Zn.**

Métodos: **17 pacientes que recibieron NPT, por pancreatitis aguda o luego de una cirugía abdominal mayor. Al inicio (To) y a la finalización (Tf) de la NPT (6 a 21 días) se determinó en suero: IL-6 y IL-6 sR (ELISA); PCR (inmunoturbidimetría); ZnPl y Zn en NPT (Espectrometría de Absorción Atómica). Características físicas: edad, años (promedio ± DE y rangos): 60,6 ± 11,7 (37-77); BMI (kg/m²): 26,0 ± 3,4 (19,9-34,0).**

Resultados: **Promedio ± DE (y rangos): aporte de Zn en la NPT: 6,1 ± 2,0 mg/día (2,8 a 10,8); parámetros bioquímicos, a To y Tf, respectivamente: Zn Pl (μg/dl): 104 ± 46 (35-177); 120 ± 55 (52-229); IL-6 (pg/mL) 93 ± 74 (10-262); 117 ± 180 (7-761); IL6sR (pg/mL): 1012 ± 322 (589-1.855); 1.269 ± 451 (631-2.195); PCR (mg/L): 71 ± 63 (2-196); 65 ± 43 (0-137).**

Dos pacientes, que fallecieron, incrementaron más de 4 veces los niveles de IL6, mantuvieron altos niveles de IL-6sR, pero disminuyendo los de PCR, recibiendo 4,2 y 5,2 mg/d de Zn. El 60% de los pacientes con evolución clínica favorable presentó una disminución de los niveles de IL6.

Conclusiones: en los pacientes críticos, con evolución favorable, dosis de Zn de 2,8 a 10,8 mg/d en la NPT no exacerbaron la respuesta inflamatoria, evaluada mediante los niveles de IL-6, IL6sR y PCR.

(*Nutr Hosp*. 2009;24:340-346)

Palabras clave: *Zinc. Pacientes críticos con nutrición parenteral. Interleuquina-6. Receptor soluble de interleuquina-6 y proteína C reactiva.*

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Recibido: 19-XII-2008.
Aceptado: 12-III-2009.

INFLUENCE OF ZINC ADMINISTERED BY TOTAL PARENTERAL NUTRITION ON PLASMATIC ZINC LEVELS, ON REACTIVE C PROTEIN, ON SERUM INTERLEUKIN-6 AND ON SERUM INTERLEUKIN-6 SOLUBLE RECEPTOR, IN CRITICAL PATIENTS

Abstract

Objectives: **To study the interrelationship between serum Interleukin-6 (IL-6), serum Interleukin-6 soluble Receptor (IL-6 sR), C-Reactive Protein (C-RP), plasmatic Zinc levels (PlZn) and their response in relation to Zn administered by TPN, in critical patients.**

Methods: **17 patients, receiving TPN as a consequence of acute pancreatitis (n = 4) or after a major abdominal surgery due to intestinal cancer (n = 7), intestinal fistula (n = 3), intestinal obstruction (n = 2) or intestinal ileus (n = 1) were studied. At the beginning (To) and at the end of the TPN administration (6-21days) serum IL-6 and IL-6 sR were determined by ELISA; C-RP ultrasensitive (C-RP us) by inmunoturbidimetric method; Zn was determined in TPN and in plasma by Atomic Absorption Spectrometry. Characteristics of the patients were (mean ± SD and ranges): age: 60.6 ± 11.7 (37-77) years; BMI (kg/m²): 26.0 ± 3.4 (19.9-34.0).**

Results: **The results (mean ± standard deviation and ranges) were: Zn provided by TPN (mg/d): 6.1 ± 2.0 (range 2.8 to 10.8). Biochemical levels were, at To and Tf, respectively: (mean±SD and ranges) were at To y Tf, respectively: Zn Pl (μg/dl): 104 ± 46 (35-177); 120 ± 55 (52-229); IL-6 (pg/mL) 93 ± 74 (10-262); 117 ± 180 (7-761); IL6sR (pg/mL): 1,012 ± 322 (589-1855); 1,269 ± 451 (631-2195); C-RP us (mg/L): 71 ± 63 (2-196); 65 ± 43 (0-137). There was no correlation between variations of IL6, IL6sR, C-RP, PlZn levels and the daily amount of Zn administered in the TPN mixtures. Two patients presented a bad evolution; they received 4.2 and 5.2 md/d of Zn and showed an increase of IL6 levels, maintained high levels of IL6sR but C-RP levels decreased**

Conclusions: **the range of 2.8 to 10.8 mg/d of Zn administered in TPN mixtures did not exacerbate the inflammatory response.**

(*Nutr Hosp*. 2009;24:340-346)

Key words: *Zinc. Critically ill patients with parenteral nutrition. Interleukin-6. Soluble receptor of interleukin-6, and C reactive protein.*

Introducción

Las cantidades de minerales que deben ser aportadas en la Nutrición Parenteral Total (NPT) presentan diferencias sustanciales con las recomendadas en la alimentación oral, ya que los nutrientes por vía parenteral llegan directamente al torrente sanguíneo. Por ello, gran parte del avance en el conocimiento de las necesidades de micronutrientes minerales, entre ellos el Zn, se ha debido a la administración de fórmulas para NPT que no tenían incorporados micronutrientes minerales o los tenían en cantidad insuficiente. En esos casos se han descrito signos clínicos y alteraciones en los niveles plasmáticos indicativos de deficiencia aguda de Zn[1,2]. Sin embargo, las recomendaciones para la administración del Zn en NPT son empíricas, difieren entre los profesionales de la salud y no hay acuerdo unánime en las distintas Sociedades Científicas, en relación a su prescripción en pacientes graves[3,4].

Las estimaciones de las necesidades de Zn aplicando el método factorial, proporcionaron información para comenzar a administrar los micronutrientes minerales en las NPT. Con esa base la AMA estableció para los pacientes adultos alimentados por vía parenteral un requerimiento de Zn de 2 a 4 mg de Zn/día[5] cifras que posteriormente sufrieron ligeras modificaciones[6]. No obstante, algunos autores han evidenciado que la adición de 4,9 a 5,6 mg/d de Zn en la NPT promueve mejores niveles de Zn plasmático y balance positivo en pacientes graves[7], ya que los pacientes que reciben NPT pueden tener aumentadas sus necesidades por el tipo de enfermedad y la medicación recibida.

Existen diversas condiciones que predisponen a la depleción del Zn, tales como: fibrosis quística, enfermedad inflamatoria intestinal, síndrome nefrótico, insuficiencia pancreática, embarazo, prematurez, síndrome de intestino corto, talasemia, uremia, o debido al uso de algunos medicamentos, como D-penicilamina[8]. Por otra parte, el conocimiento de la importancia del Zn en la cicatrización de las heridas y en la inmunidad ha llevado a los médicos a suplementar rutinariamente a pacientes catabólicos, alimentados con NPT, con dosis excesivas de Zn por vía intravenosa, similares a las que se aconsejan por vía oral (hasta 30 mg/día)[9]. El estrés metabólico puede aumentar el requerimiento de Zn en 2 mg más por día; las pérdidas elevadas de Zn en los 20 días posteriores a un trauma y las pérdidas por fístulas pueden representar varias veces los requerimientos normales, de 12 a 17 mg de Zn/L de fluído perdido[10]. En el caso particular del paciente quemado, que tiene pérdidas cutáneas de Zn muy importantes, los requerimientos pueden llegar hasta 20 mg/d[11].

Por otra parte, el exceso de Zn puede producir efectos adversos asociados con el deterioro del estado nutricional con respecto al Cu y al Fe, alteraciones en la respuesta inmune y reducción de las lipoproteínas de alta densidad. El principal efecto tóxico se debe a la interferencia con el metabolismo normal del Cu, provocando una anemia por deficiencia de Cu[8]. Además, el exceso de Zn puede provocar pancreatitis e hiperamilasemia[12] y exacerbar la fase aguda del proceso inflamatorio del paciente grave.

Al igual que otros autores[13], en un trabajo previo hemos encontrado que las mezclas de NPT elaboradas en Argentina aportaban una cantidad de Zn más elevada que la prescripta por el médico y que la cantidad agregada por el farmacéutico, de acuerdo a los protocolos de elaboración, debido a contaminación no prevista ni declarada en los componentes individuales[14].

Por otro lado, para evaluar el pronóstico de la enfermedad, en los pacientes críticos, se suele realizar, además de las medidas antropométricas y las pruebas bioquímicas e inmunológicas habituales, la medición de proteínas de fase aguda. La proteína-C reactiva (PCR) es la proteína de fase aguda mas utilizada en la clínica como indicador de gravedad y pronóstico en procesos inflamatorios y/o infecciosos[15]. En los últimos años la posibilidad de determinar algunas citoquinas ha permitido profundizar los conocimientos de la farmacocinética del Zn, permitiendo elaborar hipótesis acerca de las alteraciones metabólicas que ocurren en el paciente grave. Estos hallazgos han permitido establecer que en la fase aguda de procesos inflamatorios el Zn juega un rol importante en la liberación de Interleuquina 6 (IL-6) y de su receptor soluble (IL6sR)[16].

Por lo expuesto, es esencial que la determinación de las necesidades de micronutrientes, en particular del Zn, sea personalizada para cada paciente, teniendo en cuenta las condiciones fisiológicas y fisiopatológicas, en base a la evaluación de la función corporal y de indicadores bioquímicos[17].

Objetivos

Estudiar las variaciones de los niveles de Zn en plasma (ZnPl), de PCR, de Interleuquina-6 sérica (IL-6) y del Receptor soluble de Interleuquina-6 (sIL-6R) en relación al Zn administrado en la NPT, durante la evolución de pacientes críticos que recibían nutrición parenteral,

Materiales y métodos

Pacientes

Los pacientes estudiados que debieron recibir nutrición parenteral total (NPT) fueron atendidos por el Médico Especialista en tres centros hospitalarios privados de la Ciudad de Buenos Aires.

Las características del estudio se encuadraron en las actividades contempladas por los Comités de Docencia e Investigación de las Instituciones. El protocolo contó con la autorización de las autoridades correspondientes y fue aprobado en el marco del Proyecto UBACyT B103 de la Universidad de Buenos Aires. Se obtuvo el consentimiento informado del paciente o del familiar a

Tabla I
Características de los pacientes estudiados (n = 17)

Patología	*Pancreatitis aguda*	*Íleo/oclusión intestinal*	*Cáncer*	*Fístula intestinal*
N	4	3	7	3
Sexo	3M/1 F	1M/2F	7M	1M/2 F
		Promedio ± DE (rango)		
Edad	56,6 ± 10,0 (44-68)	51,0 ± 7,0 (44-58)	66,6 ± 6,8 (58-77)	66,7 ± 5,8 (37-74)
IMC (kg/m^2)	28,8 ± 3,7 (25,4-34,0)	23,1 ± 2,8 (19,9-25,2)	24,4 ± 4,1 (18,4-29,4)	26,5 ± 1,3 (25,0-27,3)

Sexo: M: Masculino; F: Femenino.

cargo de su cuidado, previa conversación explicativa del objetivo del estudio.

Se estudiaron 17 pacientes adultos críticos que padecían alguna de las siguientes patologías: pancreatitis aguda (n = 4), cáncer de páncreas, de cólon o de intestino (n = 7), íleo intestinal post-operatorio u obstrucción intestinal (n = 3), fístulas de bajo débito (menor a 300 ml) (n = 3) (tabla I).

En los pacientes se recolectaron muestras de sangre y de orina (de 24 horas), al comenzar la administración de la nutrición parenteral y al finalizarla (entre 10 y 21 días), con intervalos de 5-7 días. El médico con su equipo de salud efectuó el seguimiento de los pacientes y realizó la evolución clínica. Se consideró evolución favorable cuando el equipo de Terapia Nutricional indicó la suspensión de la nutrición parenteral y los pacientes comenzaron a recibir nutrición enteral u oral.

Se confeccionó una Ficha Clínica para cada paciente donde se incluyeron los datos de Laboratorio, la fórmula de la prescripción de la NPT indicada por el médico y el protocolo de su elaboración. En este protocolo figuraron, entre otros datos, las concentraciones de los nutrientes utilizados y los datos sobre el volumen diario de la fórmula administrada.

Muestras biológicas

En los pacientes se recolectaron muestras de sangre y de orina (de 24 horas), al comenzar la administración de la nutrición parenteral y al finalizarla (entre 10 y 21 días), con intervalos de 5-7 días. Se extrajo sangre, recogiendo 2 alícuotas, una con heparina, separando plasma y otra sin anticoagulante, para separar el suero.

Metodología de laboratorio

– *Zn en las fórmulas de NPT:* Las muestras de las fórmulas de NPT se mineralizaron por vía húmeda con ácido nítrico concentrado pro análisis (p.a.), utilizando bombas Parr (Nº de catálogo 4.782) y en horno de microondas. Luego de la mineralización las muestras fueron enfriadas a - 4ºC durante 1 hora y se abrieron bajo una campana con extractor de gases para ser llevadas a volumen con agua ultrapura.

– *Zn en orina y plasma:* Las determinaciones de Zn se efectuaron realizando las diluciones adecuadas con agua ultrapura. El contenido de Zn se midió por espectrofotometría de absorción atómica (VARIAN, SPECTR AA 220), con lámpara de deuterio para corrección de fondo y llama de aire-acetileno. Las condiciones de lectura fueron: 213,9 nm; slit: 1,0 nm; corriente de lámpara: 5,0 mA[18]. Rango de lectura: 0,25 a 1,5 mg/L (r = 0,9753); Se utilizaron Estándares Certificados para Zn (Riedel de Haen, Fixanal, código 498582). Los controles Interlaboratorio se realizaron en la Network EQAS Organizers (Consejería de Industria, Trabajo y Desarrollo Tecnológico), Dirección General de Trabajo, Centro de Seguridad y Salud en el Trabajo. Gobierno de Cantabria, Santander España.

Todas las determinaciones de Zn se realizaron por triplicado y las diluciones correspondientes se leyeron por duplicado. Todo el material utilizado fue tratado durante 24 horas con una solución de ácido nítrico al 20% y posteriormente lavado 6 veces con agua destilada y 6 veces con agua ultrapura (Easypure RF, compact ultrapure water system, Barnstead MΩ-cm).

Determinación de PCR, IL-6 y receptor soluble de Interleuquina-6 en suero

La Proteína C-Reactiva ultrasensible (PCR us) se determinó por inmunoturbidimetría. La Interleuquina-6 y receptor soluble de Interleuquina-6, mediante metodología de ELISA (Anogen). Para IL-6 se utilizaron 100 µL de muestra; el rango de la determinación fue de 15 a 1.500 pg/ml con un tiempo de incubación 3 horas; la sensibilidad fue menor de 2 pg/ml. Para sRIL-6 se utilizaron 150 µL de muestra; el rango de la determinación fue de 0 a 2.000 pg/ml, con un tiempo de incubación 3 horas; la sensibilidad fue menor de 7 pg/ml.

Tabla II
Valores de los parámetros bioquímicos a To y Tf

Determinaciones bioquímicas	*Valores de referencia*	*promedio ± DE y rangos*	
		To	*Tf*
ZnPl µg/dl	49-131	104 ± 46 (35-177)	120 ± 55 (52-229)
IL-6 pg/mL	< 10	113 ± 108 (10-427)	115 ± 175 (7-761)
sIL-6R pg/ml	15-48	1.210 ± 875 (589-4.385)	1.275 ± 437 (631-2.195)
PCR us mg/L	< 3	71 ± 63 (2-196)	66 ± 41 (3-137)

Análisis estadístico

Los datos descriptivos se expresaron como promedio ± desvío estándar (DE), mínimo y máximo. La comparación de medias se realizó mediante el test no paramétrico de Mann-Whitney. Se aplicó test de ANOVA, análisis de regresión y correlación simple, cuando fue necesario, con un nivel de confianza de 95%. Las comparaciones se efectuaron a través del método de Kruskal-Wallis, empleando el test de Student-Newman-Keuls[19].

Resultados

La cantidad promedio de Zn administrada diariamente a los pacientes, calculada teniendo en cuenta los datos obtenidos al determinar la concentración de Zn en las NPT y los volúmenes diarios administrados, fue (promedio ± DE y rangos): 6,1 ± 2,0 (2,8 a 10,8) mg/d**.** En todos los casos, las cantidades administradas de Zn en las NPT fueron entre 140% y 360% superiores a las prescriptas por el médico: 4,0 ± 1,2 (2,0 a 6,0) mg/d.

Los resultados (promedio ± desvío estándar y rangos, entre paréntesis) de los parámetros bioquímicos a To y Tf figuran en la tabla II. En la misma tabla se han colocado los valores de referencia de las determinaciones realizadas.

En la figura 1 se pueden observar los valores individuales de Zn plasmático al inicio (To) y al final (Tf) de la NPT y se han señalado con líneas horizontales los valores de referencia (de individuos sanos de Buenos Aires, Argentina, con adecuación nutricional)[20]. De acuerdo al promedio y rango de dichos valores de referencia, existió una gran dispersión de los datos. A To, 2 pacientes (12%) presentaron valores de ZnPl ligeramente bajos; 5 pacientes (29%) presentaron valores altos y el resto (59%) valores normales. A Tf, el ZnPl presentó valores francamente altos en 7 pacientes (41%) y valores normales en el 59% restante.

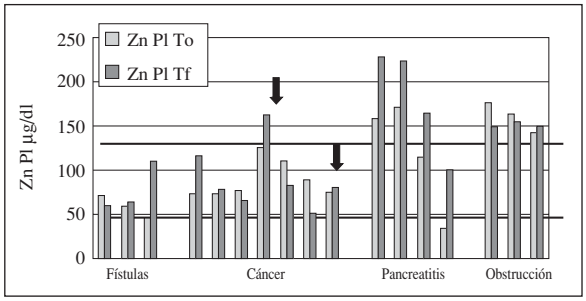

Fig. 1.—Zn Pl a To y Tf por paciente y patología, las flechas indican los pacientes que fallecieron.

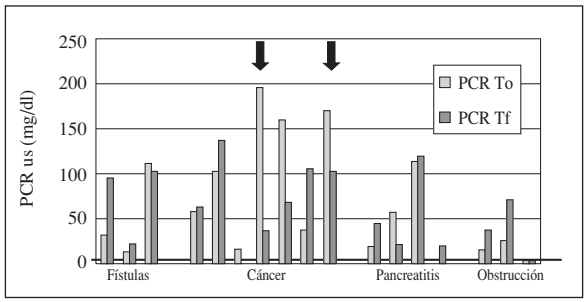

Fig. 2.—PCR a To y Tf por paciente y patología, las flechas indican los pacientes que fallecieron.

Los valores individuales de PCR a To y Tf demostraron que solo un paciente presentó niveles normales (< 3 mg/L) (fig. 2), siendo altos y variables en el resto de los casos. Los pacientes con cáncer fueron los que presentaron los valores más elevados a To. La evolución, entre To y Tf, evidenció que, durante la administración de la NPT, en 5 pacientes los valores de PCR disminuyeron y en 7 se incrementaron. Los valores de los 3 pacientes con PCR muy elevada a To disminuyeron a Tf, pese a que se mantuvieron muy elevados, y 2 de ellos fallecieron.

En la figura 3 se han representado los valores individuales de IL-6 a To y Tf. Los valores de IL-6 a To en todos los pacientes, excepto en uno, fueron superiores al valor normal (10 pg/mL). A Tf la IL-6 disminuyó en

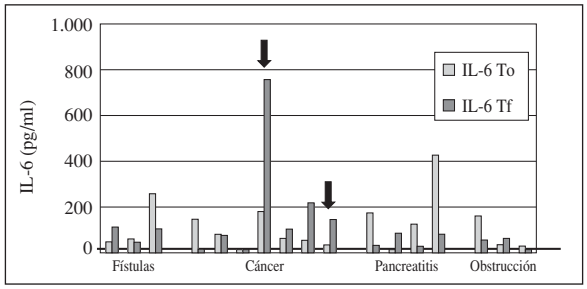

Fig. 3.—IL-6 a To y Tf por paciente y patología, las flechas indican los pacientes que fallecieron.

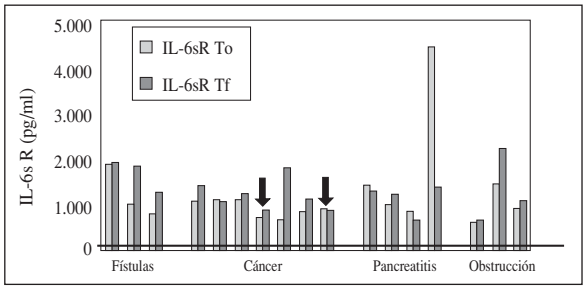

Fig. 4.—slL6R a To y Tf por paciente y patología, las flechas indican los pacientes que fallecieron.

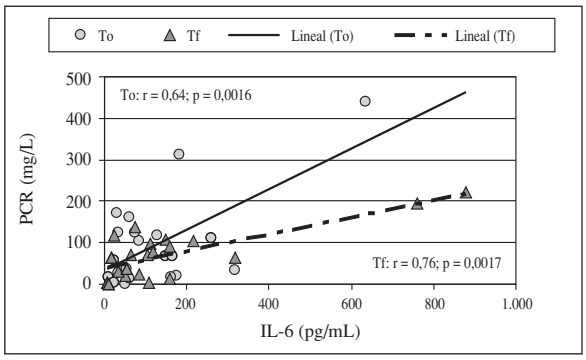

Fig. 5.—PCR vs *IL6 a To y Tf.*

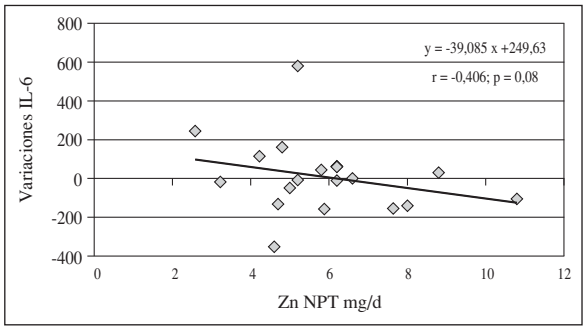

Fig. 6.—Variaciones IL-6 vs *ZnTPN.*

9 pacientes y aumentó en 7. De aquellos que aumentaron, 3 presentaron valores muy altos (147 a 761 pg/ml) y 2 de estos últimos fallecieron.

En la figura 4 se han representado los valores individuales de sIL-6R a To y Tf. Los valores de sIL-6R fueron elevados en todos los pacientes tanto a To como a Tf. Se debe destacar que fallecieron 2 pacientes de los 4 que a Tf presentaron los valores más bajos (631 a 874).

Los niveles de IL-6 correlacionaron positivamente con los de PCR tanto a To como a Tf, aunque las pendientes fueron diferentes (fig. 5) y las variaciones de IL-6 mostraron una significativa correlación inversa con las variaciones de PCR (r = - 0,55; p = 0,010).

La variación de IL-6 en función del Zn en la NPT (mg/d) mostró una débil correlación inversa (r = - 0,406; p = 0,08) con el Zn administrado en la NPT, en el rango de 2,8 a 10,8 mg/d (fig. 6).

Discusión

La cantidad promedio de Zn administrada diariamente a los pacientes, en las mezclas de NPT preparadas, fue entre 140% y 360% superior a la prescriptas por el médico. Estos datos concuerdan con otros autores[13], y con nuestros resultados previos que demostraron contaminación no prevista ni declarada en los componentes individuales utilizados para la elaboración de las mezclas de NPT[14]. Esos resultados evidenciaron Zn en 16 componentes (especialidades medicinales de laboratorios nacionales, de Estados Unidos y Alemania), con valores variables según el fabricante, la fecha de fabricación y el lote de cada producto. La solución de dextrosa y los lípidos presentaron las mayores cantidades de contaminación con Zn y todas las soluciones de sulfato de cobre (n = 6) contenían Zn, no declarado en los rótulos. Por lo tanto, las mezclas de NPT de prescripción habitual en Argentina alcanzan una concentración final de Zn superior a la prescripción médica, a la cantidad colocada por los farmacéuticos según la información de los rótulos, y a las recomendaciones internacionales. Esas cantidades halladas de Zn no producirían inconvenientes en pacientes clínicamente estables, pero deberían ser tenidas en cuenta en aquellos con enfermedades inflamatorias, insuficiencia renal, alteración hepática o colestasis.

En la figura 1 se puede observar que al inicio de la NPT (To), los niveles de Zn plasmático (ZnPl) fueron sumamente variables, indicando la respuesta individual de redistribución del Zn corporal de cada paciente a consecuencia del estrés de su patología y, en algunos casos, de la cirugía. En el caso de pacientes graves, la presencia de infección, inflamación y daño tisular producen captación de Zn por el hígado, médula ósea y timo, disminuyendo el Zn en plasma para favorecer la liberación de citoquinas (factor de necrosis tumoral, IL1, IL6) y proteínas de fase aguda[21]. Por ello, se han documentado valores bajos de ZnPl en pacientes graves, debido a dichas alteraciones metabólicas, que no indican riesgo de deficiencia clínica. Sin embargo, a pesar de las patologías y la gravedad de los pacientes estudiados en este trabajo, sólo 2 de ellos presentaron a To valores de ZnPl inferiores al rango de normalidad, 5 fueron altos y el resto presentó valores normales. Además, a Tf, solo 1 paciente presentó valores ligeramente inferiores al rango de normalidad y 7 pacientes valores muy elevados, manteniéndose en valores normales en el resto. Estos resultados de los valores de ZnPl estarían indicando que no existió deficiencia de Zn previa a la administración de la NPT. Los niveles elevados de ZnPl a Tf podrían indicar un exceso en la cantidad administrada en la NPT, con la posibilidad de que se presenten efectos adversos. Estos efectos adversos deben ser evitados para no comprometer la recuperación del paciente grave, ya que el exceso de Zn produce supresión de la respuesta inmune y deterioro del estado nutricional con respecto al Cu y al Fe[8].

Durante el tratamiento con NPT, no se evidenció correlación entre las variaciones de los valores de ZnPl y el Zn administrado en la NPT. Por consiguiente, los niveles plasmáticos de Zn no constituyeron un indicador adecuado para establecer las dosis de Zn a prescribir en la NPT del paciente grave. Sin embargo, a Tf los pacientes con valores altos no normalizaron sus niveles plasmáticos, posiblemente por haber recibido cantidades superiores a las prescriptas (promedio 6,9 mg/d), debido a la contaminación no prevista de los componentes utilizados para la preparación. Por consiguiente, los niveles plasmáticos de Zn en función del Zn administrado en la NPT, no constituyeron un indicador adecuado para establecer las dosis de Zn a prescribir en la NPT del paciente grave, tal como de evidenció en una publicación previa donde se estudiaron 29 pacientes criticos[22].

Con el objetivo de visualizar si existía una exacerbación de la respuesta de fase aguda de los pacientes graves estudiados de acuerdo a la concentración de Zn en las mezclas, se evaluó la respuesta del proceso inflamatorio y la evolución de los pacientes, a través de los niveles de la PCR, de IL-6 y del sIL-6 R, analizando las interrelaciones entre las variaciones de dichos indicadores y las dosis de Zn administrado, durante el período que recibieron la NPT.

La liberación de IL-6 se debe al aumento de actividad del sistema monocito-macrófago, aunque podría haber otros lugares de síntesis de IL-6 como los fibroblastos, las células endoteliales o los adipocitos[23]. Otros trabajos en pacientes con procesos inflamatorios graves (artritis reumatoidea) han evidenciado que la liberación de IL-6 precede a la de PCR y favorece su liberación[24], indicando que la IL-6 es indicador de pronóstico de evolución, mientras que la PCR indica el mantenimiento del proceso inflamatorio. En pacientes con pancreatitis aguda también se ha comprobado que el aumento de los niveles de IL-6 precede a la liberación de PCR y, por lo tanto, es mejor predictor de evolución que la proteína C-Reactiva[23].

Los resultados del presente trabajo concuerdan con los trabajos mencionados. La correlación positiva entre los niveles de IL-6 y los de PCR a To y a Tf indican que ambos indicadores evolucionaron en el mismo sentido durante todo el período de tratamiento de los pacientes graves con NPT. Por otra parte, la mayor pendiente a To que a Tf indica que la PCR disminuyó más rápidamente que la IL-6 y, explican la correlación inversa entre las variaciones de PCR y las variaciones de IL-6 ($r = -0,55$; $p = 0,010$). Los 2 pacientes que fallecieron presentaron un gran incremento de la IL-6 entre To y Tf, pero la PCR disminuyó aunque se mantuvo en valores elevados, lo que demuestra que el aumento de los niveles de IL-6 precede a la liberación de PCR y, por lo tanto, es mejor predictor de evolución que la proteina C-Reactiva.

Los 2 pacientes que presentaron muy mala evolución clínica, incrementaron más de 4 veces los niveles de IL-6 y fallecieron, a pesar de haber recibido solamente entre 2,8 y 5,2 mg de Zn por día (incluída la contaminación). Los pacientes con evolución clínica favorable presentaron a Tf en el 60% de los casos una disminución de los niveles de IL-6, y los restantes pacientes presentaron leve aumento de la respuesta de la IL-6, aún recibiendo hasta 8,4 mg de Zn/d.

La IL-6 transmite las señales a las células mediante 2 mecanismos: 1) uniéndose al receptor en la superficie celular, en hepatocitos, monocitos, macrófagos y algunos monocitos; 2) mediante la forma soluble del receptor (sIL-6R) que interviene en la transducción de la señal para ejercer su acción en las células que no tienen receptores transmembrana, como las articulaciones o en otras células involucradas en la respuesta inflamatoria. En pacientes con artritis reumatoidea se ha evidenciado que la IL-6 y su receptor son mediadores claves en la respuesta sistémica y en las manifestaciones locales de esa patología, lo cual ha llevando a ensayar bloqueadores del receptor (sIL-6R) para controlar la enfermedad[24].

En este estudio los dos pacientes que presentaron mala evolución clínica, tuvieron niveles altos de sIL-6R a To y se mantuvieron elevados a Tf, lo cual indica que el receptor soluble también se comporta como un indicador de gravedad. Se debe destacar que, si bien todos los valores del sIL-6R se mantuvieron altos, 4 pacientes tuvieron valores más bajos a Tf y 2 de estos últimos fueron los que fallecieron.

Pese a que durante el tratamiento con NPT, no se evidenció correlación entre las variaciones de los valores plasmáticos de Zn (ZnPl) y el Zn administrado en la NPT, existió una correlación inversa entre las variaciones de IL-6 y las del sIL-6R con las variaciones de ZnPl ($r = -0,486$; $p = 0,04$ y $r = -0,542$; $p = 0,04$, respectivamente). Estos resultados están de acuerdo con la hipótesis de que la disminución de los niveles de ZnPl durante los procesos inflamatorios es consecuencia del pasaje del Zn a los tejidos para la formación de citoquinas (IL-1, IL-6 y FNT) como proteínas de fase aguda. Además, se confirma lo evidenciado en un trabajo previo donde hemos demostrado que las determinaciones de zinc eritrocitario serían de mayor utilidad que el Zn plasmático para controlar los niveles de zinc administrados en la nutrición parenteral a pacientes graves[22].

Por otra parte, la correlación inversa entre la variación de IL-6 y la cantidad de Zn administrado en la NPT en el rango de 2,8 a 10,8 mg/d de Zn en la NPT, indica que 6 pacientes que recibieron entre 2,4 y 6 mg de Zn/d presentaron aumento de la IL-6 y que los pacientes que recibieron entre 6 y 10,8 mg de Zn/d disminuyeron en todos los casos los niveles de IL-6 lo que es pronóstico de buena evolución. Por lo tanto, esos pacientes que recibieron las mayores dosis de Zn, hasta más de 3 veces la cantidad prescripta en las NPT (10,8 mg/día, por la presencia de contaminación no contemplada), no mostraron un efecto perjudicial en la evolución de los indicadores de la respuesta inflamatoria, lo cual indica que las cantidades de Zn administrado no fueron excesivas. Estos resultados están de acuerdo con evidencias acerca del

efecto beneficioso, en pacientes con catabolismo aumentado, de un adicional de 2 a 4 mg/día de Zn sobre las recomendaciones estándar[25].

Por otra parte, en estos pacientes graves, las pérdidas urinarias fueron muy variables y presentaron una gran dispersión: promedio ± DE de 2,2 ±1,7 mg/d, oscilando entre 0,3 y 4,4 mg/d. Por lo tanto, cantidades entre 8,1 y 10,8 mg/día de Zn, que son la suma del prescrito mas el de la contaminación (de los componentes), podrían ser necesarias en algunos pacientes graves para compensar las pérdidas urinarias.

Conclusiones

1) A pesar de los recaudos para prescribir a los pacientes la dosis recomendada de Zn (2,5-5 mg/d), las cantidades administradas en las NPT fueron superiores a las prescriptas, debido a la contaminación inevitable de las materias primas.

2) Teniendo en cuenta que los pacientes estudiados padecían diferentes patologías y que, la respuesta de los indicadores bioquímicos determinados fue variable ante diferentes cantidades de Zn administrada, podríamos concluír que:

- La correlación inversa entre la variación de IL-6 y las cantidades de Zn administrado en la NPT indicaría que entre 4,6 y 10,8 mg de Zn/día serían cantidades adecuadas para los pacientes estudiados con evolución favorable, ya que en ese rango existió una disminución de la IL-6.
- Los pacientes estudiados, excepto 2 que fallecieron, tuvieron evolución favorable a pesar de presentar elevados niveles de IL-6, sIL-6R y de PCR, debido a la persistencia de la gravedad del proceso inflamatorio.
- En el caso de los pacientes graves con NPT las dosis óptimas de Zn a administrar, oscilarían entre 6 y 10 mg/d, dado que no existió respuesta indeseable en ninguno de ellos. Además, considerando la contaminación inevitable de los componentes utilizados en la preparación de la NPT, los médicos deberían prescribir cantidades de Zn de 4,2 a 7 mg/día en el caso de los pacientes críticos.

Referencias

1. Greene HL, Hambidge MD, Schandler R and Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subconmmittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition. *Am J Clin Nutr* 1988; 48: 1324-42.
2. Forbes G y cols. Micronutrient status in Patients Receiving Home Parenteral Nutrition. *Nutrition* 1997: 11-12.
3. Braunschweig CA. Trace elements and the acute Phase response: Implications for Nutrition Support. Postgraduate course. Washington DC, USA: Ed. American Society for Parenteral and Enteral Nutrition; 1996: 9-20.
4. Shenkin A, Allwood MC. Oligoelementos y vitaminas en la nutrición intravenosa en adultos. Capítulo 4. En: Nutrición Clínica. Rombeau JL, Rollandelli RH (eds.). Nutrición Clínica Nutrición Parenteral. México DF: McGraw-Hill Interamericana; 2002: 65-86.
5. American Medical Association, Departament of Foods and Nutrition —1979b— Guidelines for essencial trace element preparations for parenteral use: A statement by an expert panel. *JAMA* 1979; 241 (19): 2051-2054.
6. Fleming CR. Trace elements metabolism in adult patients requiring total parenteral nutrition. *Am J Clin Nutr* 1989 (49): 573-9.
7. Prelack K, Sheridan L. Micronutrient Supplementation in the critically III Patient: Strategies for Clinical Practice. *J Trauma* 2001; 3 (51): 601-620.
8. Solomons, NW. Zinc, Trace Elementos. En: Clinincal Guide to Parenteral Micronutrition Thomas G Baumgartner (ed.). Chapter 9. Second Edition. USA: Lyphomed; 1991: 216-231.
9. King JC, Keen CL. Zinc. Chapter 10. In: Modern Nutrition in health and disease. Shils ME et al. Eighth Edition. Malvern, PA, USA: Lea & Febiger; 1994: 214-230.
10. Leung FY. Trace Element in Parenteral Nutrition. *Clinical Biochemistry* 199?; 28 (6): 562-66.
11. Henzel JH, De Weese MS, Pories MW. Significance of mangnesium and Zinc metabolism in the surgical patients. *Arch Surg* 1967; 9: 991-999.
12. Brocks A, Reid H, Glazer G. Acute intravenous Zinc poisoning. *Br Med J* 1977; 1: 1390-1.
13. Pluhator-Murton M y cols. Trace element contamination of Total Parenteral Nutrition. 1 Contribution of Component Solutions. *Journal of Parenteral and Enteral Nutrition* 1999; 23 (4): 222-227.
14. Menéndez AM, Weisstaub A, Montemerlo H, Rusi F, Guidoni ME, Piñeiro A, Portela ML. Contenido de zinc y cobre en los componentes individuales en las mezclas para fórmulas pediátricas de Nutrición Parenteral Total. *Nutric Hosp* 2007; 22 (5): 545-551.
15. García Lorenzo y Mateos A, López Martínez J, Sánchez Castilla M. Respuesta inflamatoria sistémica: definiciones, marcadores inflamatorios y posibilidades terapéuticas. *Medicina Intensiva* 2000; 24 (8): 361-70.
16. Rink L, Kirchner H. Zinc-Altered immune function and cytokine production. *J Nutr* 2000; (130): 1408S-1411S.
17. ASPEN Board. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. *JPEN* 2002; (25): 31SA.
18. Perkin Elmer Corp. Analytical method for atomic absorption spectrophotometry. Perkin Elmer Corp. Norwalk C.T, 1971.
19. Dawson-Saunders and Trapp R. Bioestadística Médica. 1°.ed. Editorial El Manual Moderno; México DF, 1994.
20. Weisstaub AR, Menéndez AM, Montemerlo H, Pastene H, Piñeiro A, Guidoni ME, Pita Martín de Portela ML. Zinc plasmático, cobre sérico y zinc y cobre eritrocitarios en adultos sanos de Buenos Aires. *Acta Bioquímica Clínica* 2008: 42 (3). En prensa.
21. Cousins R and Hempe JM. Cinc. En: Present Knowledge in Nutrition, 6th ed., Chap. 28. M.L.Brown. Washington, D.C., USA: Ed. Nutrition Foundation; 1990: 289-308.
22. Menéndez AM, Weisstaub A, Montemerlo H, Alloatti S, Guidoni ME, Rusi F, Portela ML. Relación entre las cantidades de cobre y zinc administradas a pacientes graves con Nutrición Parenteral Total y los niveles de cobre y zinc en plasma y eritrocitos. *Nutric Hosp* 2008: 23 (4): 373-382.
23. Leser HG, Gross V, Scheibenbogen A, Heinisch A, Salm R, Lausen K, Rückauer R, Andreesen R, Farthmann EH, Schölmerich J. Elevation of serum interleukin-6 concentration preceds acute-phase response and reflects severity in acute pancreatitis. *Gastroenterology* 1991; (101): 782-785.
24. Tadamitsu Kishimoto. Interleukin-6: discovery of pleiotropic cytokine. *Arthritis Research Therapy* 2006; 8 (Supl. 2): 1-6.
25. Braunschweig CL, Sowers M, Kovacevich DS, Gretchen M, August DA. Parental Zinc supplementation in adult humans during the acute phase response increases the febril response. *J Nutr* 1997; (127): 70-74.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):347-353
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Trends in home enteral nutrition in Spain; analysis of the NADYA registry 1992-2007

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Abstract

Background: **There are few data on trends in home enteral nutrition (HEN) practice in different countries. NADYA is the Spanish home artificial nutrition (HAN) group, and is responsible for the Spanish HAN registry.**

Method: **We performed a 16-year retrospective study (1992-2007) of the Spanish HEN registry by retrieving data from the NADYA database and from publications of the working group. People receiving more than 1000 kcal/d with an enteral formula were included regardless of the access route (oral/tube feeding).**

Results: **The number of patients registered increased more than 8 times during the study period: the current prevalence is 113 patients/10^6 inhabitants (oral and tube feeding), or 41 patients/10^6 inhabitants (tube feeding). The distribution of the patients was not uniform, and most came from six autonomous communities (Catalonia, Galicia, Castilla-León, Madrid, Andalusia and Extremadura). Gender distribution was nearly 1:1. The number of paediatric patients was very low, representing less than 10% of the total. Mean age in adults was above 65 years in most of the reports. We observed an increase in the age of the patients over the years. The most common underlying diseases were neurological disorders, followed by cancer. We observed an increase in the use of the oral route, from 5.8% in 1992 to 64% in 2007, with a parallel decrease in the use of nasogastric tubes. Gastrostomy tubes were used in 15-20% of the patients. The number of complications was low (less than one complication/patient/year), the most frequent being change of tube, followed by gastrointestinal complications. The principal reasons for discontinuing treatment were death related to the underlying disease (40-50%) and switch to oral diet (30-40%). Most of the patients (75%) were followed by the hospital nutrition unit. Provision of the enteral formula and disposables varied according to the autonomous community. Most of the patients had limited physical activity or were chair- or bed-bound, requiring partial or total help in their daily life.**

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Recibido: 01-II-2009.
Aceptado: 09-II-2009.

TENDENCIAS EN NUTRICIÓN ENTERAL DOMICILIARIA EN ESPAÑA; ANÁLISIS DEL REGISTRO NADYA 1992-2007

Resumen

Introducción: **Existen pocos datos sobre la evolución de la práctica de la nutrición enteral domiciliaria (NED) en diferentes países. NADYA es el grupo de trabajo español de nutrición artificial domiciliaria (NAD), y es responsable del registro español de estos pacientes.**

Métodos: **Realizamos un estudio retrospectivo de los últimos 16 años (1992-2007) del registro español de NED utilizando la base de datos de NADYA y las publicaciones del grupo de trabajo. Se incluyeron aquellos pacientes que recibieron más de 1000 kcal/d de una fórmula enteral, independientemente de la vía de acceso (oral/sonda).**

Resultados: **El número de pacientes registrados se multiplicó por ocho durante el periodo de estudio: prevalencia actual 113 pacientes/10^6 habitantes (oral y sonda), o 41 pacientes/10^6 habitantes (sonda). La distribución de los pacientes no fue uniforme, y la mayoría pertenecían a seis comunidades autónomas (Cataluña, Galicia, Castilla-León, Madrid, Andalucía y Extremadura). La distribución por sexo fue casi 1:1. El número de pacientes pediátricos fue muy bajo, representando menos del 10% del total. La edad media de los adultos fue superior a 65 años en la mayoría de los registros. Observamos un incremento en la edad de los pacientes a lo largo de los años de estudio. Las enfermedades más prevalentes fueron las neurológicas, seguidas del cáncer. Observamos un aumento del uso de la nutrición enteral oral, de 5,8% en 1992 a 64% en 2007, con un descenso paralelo del uso de las sondas nasogástricas. La gastrostomía se utilizó en el 15-20% de los pacientes. El número de complicaciones fue bajo (menos de una complicación/paciente/año), siendo la más frecuente el cambio de la sonda, seguida de las complicaciones gastrointestinales. Las principales razones de finalización del tratamiento fueron la muerte relacionada con la patología de base (40-50%) y el paso a la alimentación oral (30-40%). La mayoría de los pacientes (75%) fueron seguidos por las unidades de nutrición de los hospitales. El suministro de la fórmula de nutrición enteral y el material fungible varió dependiendo de las comunidades autónomas. La mayoría de los pacientes tenían limitada su actividad física o estaban confinados a cama/sillón, y requerían ayuda total o parcial para las actividades de la vida diaria.**

Conclusions: **The use of HEN has increased dramatically in the last 16 years in Spain. Most of the patients registered were elderly people with neurological disorders and limited physical activity. The oral route was the most frequently used. The number of complications was low. The mortality rate in these patients was highly related to the underlying disease.**

(*Nutr Hosp*. 2009;24:347-353)

Key words: *Home enteral nutrition. Registry. Complications.*

Conclusiones: **El uso de la NED ha aumentado mucho en los últimos 16 años en España. La mayoría de los pacientes registrados eran ancianos con enfermedades neurológicas y con una limitada actividad física. La vía oral fue la más empleada. El número de complicaciones fue bajo. La mortalidad de estos pacientes se relacionó principalmente con la enfermedad de base.**

(*Nutr Hosp*. 2009;24:347-353)

Palabras clave: *Nutrición enteral domiciliaria. Registro. Complicaciones.*

Introduction

Home enteral nutrition (HEN) is defined as the provision of enteral diets as the main source of daily intake at home. However, there is little agreement about what constitutes HEN. In one European survey, three countries (Italy, France, United Kingdom) considered only tube feedings covering > 75% of requirements as enteral nutrition, and six countries considered both tube and oral feedings covering > 75% requirements as enteral nutrition (Belgium, Czech Republic, Denmark, Israel, Poland, Spain). In two countries (Austria, Croatia), any kind of enteral diet or supplement was considered as enteral nutrition.[1]

The use of HEN has increased enormously in the last few decades,[2,3] triggering the development of specific legislation, guidelines and national registries in many countries.[1]

The Spanish home artificial nutrition (HAN) group, NADYA, was established in 1992 by health care professionals working with artificial nutrition.[4] One of the aims of the group has been the maintenance of a voluntary registry, which is accessible at www.nadya-senpe.com.

We now have an extensive database on the practice of HAN in Spain. Since 1994, the annual registries of patients on HAN have been published periodically (with the exception of 1997 and 1998), and we have observed an increase in the number of patients registered.[5-14] In 2006 we reviewed the progress of home parenteral nutrition (HPN) through this registry.[15] In this article, we present trends in HEN practice in Spain during this period.

Material and methods

We performed a 16-year retrospective study (1992-2007) evaluating the characteristics of patients receiving HEN in Spain. The data were extracted from the NADYA registry, and most are available in yearly publications.[5-14] The NADYA registry is voluntary and depends on the goodwill of reporters; therefore, real data may be underreported.

In1992, our group performed a national survey on HEN practice.[16] The first registry was conducted in 1994[5] and yearly thereafter, except for the years 1997-1998 (not available). Data from the years 2004 and 2005 are partial because of changes in the organization of the registry.[17] Data included personal information, underlying disease, type of enteral access, length of treatment, complications, outcome, HEN providers, physical activity, and patient autonomy. As the data from the previous year were filled out at the end of the current year, the prevalence was calculated annually.

Data recording in the initial registry was on paper until 1998, when an on-line reporting system was set up on the group's website, thus providing reporting physicians with direct individual access to the registry. The patients included in the registry were those receiving more than 1,000 kcal/d with an enteral formula regardless of the access route (oral/tube feeding).

In 2005, the registry was updated to meet the stipulations of Data Protection Law 15/1999, and changes were made: the number of items was reduced in order to increase the participation of the investigators.[17] Furthermore, in the updated version, data can be entered at any time, and are available until the investigator closes the enteral episode.

Results

Period prevalence 1992-2007

The number of patients registered increased more than 8 times during the study period (fig. 1). In 2007, the prevalence was 113 patients/10^6 inhabitants (including oral and tube feeding), or 41 patients/10^6 inhabitants (including only tube feeding).[14] The number of reporting centres during this period varied from 17 in 1994 to 28 in 2007.

In the period 2004-2005 there was a decrease in the number of patients registered due to the changes in the working of the registry.

Interestingly, the distribution of patients throughout Spain in not uniform (fig. 2). The available data from 10 of the 17 autonomous communities show that most patients were in six communities (Catalonia, Galicia, Castilla-León, Madrid, Andalusia, Extremadura).

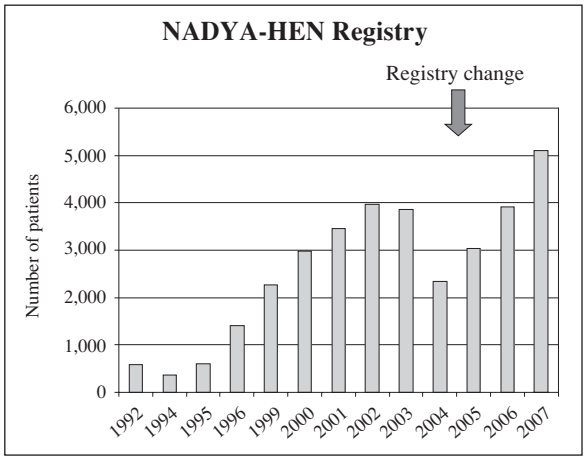

Fig. 1.—Evolution of the number of patients in the NADYA-HEN registry during the period 1992-2007.

Gender distribution was nearly 1:1, and the number of paediatric patients was very low (less than 10% of the registry). The mean age in adults is above 65 years in most reports (68 yrs in 2007); in children it is 4-6 years (4.2 yrs in 2007). Age tended to increase during the study period: people older than 74 years made up 26% of the study population in 1994, compared with 42% in 2007.

Underlying disease

Neurological disorders and cancer were the two most prevalent diagnoses, affecting nearly 70% of the patients (table I). In the last few years of the study period, we observed an increase in the number of patients with neurological diseases over cancer, probably as a result of the older age of the patients registered. Gastrointestinal diseases (eg, inflammatory bowel disease, motility disorders, malabsorption, ischemia, and radiation enteritis) represented less than 5%. During the last 5 years, HIV infection was present in very few patients.

Enteral access route

There was a large increase in the use of the oral route during the study period, from 5.8% in 1992 to 64% in 2007, with a parallel decrease in the use of nasogastric tubes, from 68.8% in 1992 to 26% in 2007. Gastrostomy tubes were used in 15-20% of patients, representing 25% of non-oral accesses. Jejunostomy tubes were used in 2% of patients.

Length of treatment

We observed an increase in the length of treatment from 6.3 months in 1994 to 9.4 months in 2007. Before the modification of the registry in 2005, the duration of treatment was < 3 months in ~30% of patients and between 3 and 5 months in 20%. This trend changed during the last few years of the study.

Complications

All the data on complications come from the old registry (table II). In general, patients had less than one HEN-related complication per year. The most frequent

Fig. 2.— Prevalence of HEN according to autonomous communities in 2007 (expressed per million inhabitants).

Table I
Diagnosis of patients requiring HEN in the NADYA registry (data are expressed as a percentage)

	Cancer	*Neurological disorders*	*Gastrointestinal diseases*	*AIDS*	*Other diagnosis*
1992	45	32	8		15
1994	36	35	7.6	1	21.4
1995	41	33.5	5.7	2.9	16.9
1996	39	33	5	3	20
1999	36.8	37.5	5.5	3.6	16.6
2000	32	41	4		23
2001	33.5	43.5	4	3	16
2002	35	39	3	3	20
2003	39	37.4			23.6
2004	29	40	4	–	27
2005	30	41	5	–	24
2006	28	42	4	–	26
2007	28	37	4	–	31

was the change of enteral tube, followed by gastrointestinal complications (diarrhoea, constipation).

Outcome

Until 2003, between 30% and 40% of patients were weaned from HEN during the year. This percentage fell towards the end of the study probably due to misreporting of data (ie, the investigators did not close the episodes). The principal reasons for discontinuing treatment were death related to the underlying disease (40-50%) and progress to oral diet (30-40%). Approximately 10-15% patients were lost to follow-up.

Follow-up and delivery of treatment

In 75% of patients, follow-up was performed by the hospital nutrition unit and in 10-15% by the home hospitalization units.

The enteral formula was provided by the hospital and private pharmacies, depending on the area. The type of formula was recorded until 2003, and polymeric formulas were the most commonly used (85%). The disposables were mainly provided by the hospitals. Enteral pumps were used in only 10% of patients.

Physical activity and autonomy

Most of the patients were limited in their physical activity (30%), or were chair- or bed-bound (40%). Very few patients were unconscious (1%). Most adult patients required partial (28%) or total help (39%) in their daily activities.

Discussion

We describe HEN practice in Spain over a 16-year period. The information we provide is useful, given

Table II
Complications of HEN (complications/patient/year)

	Total number	*Mechanic*	*Metabolic*	*Gastrointestinal*	*Tube change*
1992	0.18				
1994	0.07	0.04	0.005	0.002	
1995	0.5	0.09	0.003	0.17	0.23
1996	0.74	0.19	0.01	0.28	0.28
1999	0.62	0.12	0.01	0.26	0.25
2000	0.75	0.19	0.007	0.25	0.3
2001		0.15		0.16	
2002	0.85	0.19	0.078	0.25	0.32
2003	0.63	0.14	0.02	0.19	0.28

that HEN has received less attention in the literature than HPN.

We observed an enormous increase in HEN during the study period. This increase is the result of the development of the enteral industry (including new enteral formulas, many of them for oral use, and improvements in enteral access) and legislation on HEN, and a growing awareness of the importance of malnutrition in the prognosis of illness.

HEN was first approved in Spain in 1998 for people incapable of covering their daily requirements by oral diets.[18] Enteral feeding (generally by tube) is publicly financed for a long list of diseases. Legislation has recently been modified,[19] and in 1998, a group of experts on HEN and the Ministry of Health developed national guidelines,[20] which have recently been updated.[21]

As the NADYA registry is voluntary, we are aware that it could underestimate the number of patients on HEN in Spain. This is clearly visible from the map of the Spanish autonomous communities (fig. 2). The different systems for organizing HEN make follow-up easier to perform in some autonomous communities (for example Catalonia and Galicia).

Our data show that the prevalence of HEN is 113 patients/10^6 inhabitants (including oral and tube feeding), or 41 patients/10^6 inhabitants (including only tube feeding). Except for 5 autonomous communities (Catalonia, Galicia, Castilla-León, Madrid, Andalusia), this prevalence is lower than observed in other studies performed in different areas of Spain.

In Valladolid, de Luis et al[22] reported an incidence of 95-265 patients/10^6 inhabitants in the period 1999-2004. In Galicia, the prevalence found in a multicentre study in 1998-1999 was much higher (1,034 cases/10^6 inhabitants).[23] Although several studies have shown an increase in HEN in other areas of Spain, prevalence is unknown.[24-26]

In Europe, the prevalence of HEN is also unknown. One European survey in 1999, reported the median annual incidence to be 163 patients/10^6 inhabitants/year (range 62-457).[3] The British registry, which includes only people on tube feeding, reported 24,203 adult patients (prevalence 404 cases/million) and 5,831 children in 2007.[27] In Germany, the number of patients on HEN is unknown, but probably exceeds 100,000 cases.[28] An Italian survey in 2005 showed a prevalence of 128 cases/million.[29] In a recent report from Northeast Italy, the mean incidence and prevalence of HEN during 2001-2005 were 308.7 and 379.8 cases/million, respectively.[30] In the United States, there were 152,000 patients on HEN in 1992, with a prevalence of 415 cases/million during 1989-1992.[2]

Neurological disorders and cancer are the most frequent indications for HEN in our registry. The first has increased over the years, probably as a result of aging of the population. These data are similar to those from two studies performed in Galicia,[23,31] but differ from those reported in the study from Valladolid,[22] in which head and neck cancer was the most common underlying disease (43.8%), and neurological disorders represented only 9.6%, probably as a result of the younger age of the patients included (mean age 56.4 yrs).

In the European survey, the most frequent diagnoses were neurological disorders and head and neck cancer.[3] In the British registry, which includes patients with very similar characteristics to ours, neurological disorders were also the most frequent diseases.[27] In Italy, most patients on HEN had neurological disorders.[29,30] In the North American Home Parenteral and Enteral Nutrition Registry 1985-1992, the most frequent diagnosis was cancer (40%) followed by dysphagia (30%).[2] More recent data from Denver on 17,014 patients (mean age 46.6 years) followed from 1998 to 2002 showed that the most common indications were gastrointestinal diseases, malnutrition, and diseases of the esophagus.[32] The indication for HEN is clearly shown to depend on the characteristics of the patients (mainly age).

In our series, oral enteral feeding was the most frequently used approach, especially in the latter part of the study, as a result of the enormous increase in the availability of oral formulas during this period. This mirrors the results of the studies from Galicia[23,31] and Valladolid,[22] but differs from the practice in areas where oral enteral feeding is not reimbursed[28,32] and the patients are not included in the national registries.[2,27]

The use of gastrostomy tubes in our series was very low (15-20%) —25% of non-oral feedings— especially taking into account the age of the patients and the underlying disease. This percentage is similar to that observed in studies from other areas of Spain,[22,23,31] but differs from those reported in other countries (58.2% of gastrostomies in the European survey, 83% in the British registry).[3,27] However, in the study from Northeast Italy, most patients were fed by nasogastric tube.[30] In the United States, gastrostomies are probably overused because Medicare only finances HEN treatment lasting more than 3 months.[33] In addition, these tubes are currently very common in nursing homes.[32] In 1989, 15,000 percutaneous endoscopic gastrostomy (PEG) tubes were used; in 2000, this figure had risen to more than 216,000 tubes. Approximately 30% were used in patients with dementia.[34]

Although gastrostomy is indicated in long-term enteral feeding because of its safety and patient comfort,[35] there are many doubts over its benefits in some cases, especially in patients with advanced dementia.[36,37]

The number of complications in our registry was low, the most frequent being change of the feeding tube. This could be avoided by the use of gastrostomy in some cases. Our complication rate is similar to those of other studies performed in Spain[22,23,31,38] and elsewhere.[2,39,40]

The increase in the length of treatment over the years in our series is probably unreal and may reflect misreporting of the weaning process during follow-up in the

new registry. The most frequent reasons for discontinuing treatment were death and progress to oral diet, as occurred in other series.[2,22,27,30] It is important to note that mortality is very high (20% mortality 1 month after starting treatment) despite appropriate selection of patients,[41] and mostly depends on age and underlying disease.[22,42,43]

In our experience, HEN was used in elderly people (most of them chair- or bed-bound) who required partial or total help in their daily activities. These features are common in the British registry.[27]

The organization of HEN in Spain differs according to the autonomous community. While the enteral formula and disposables are provided by the hospital (or directly delivered to the patient's home through agreements with the enteral feeding industry) in Galicia and Catalonia, in the rest of the country the formula is provided by private pharmacies and the disposables by the hospital or primary care centers.

As this treatment is financed by the National Health Services in many countries, it is important to establish its cost-effectiveness. HEN costs about a tenth of HPN. In a recent report from Elia et al,[44] the cost per quality adjusted life years in patients receiving long-term enteral tube feeding in their own home was £ 12,817. This cost compares favourably with other forms of intervention, and is well within the typical range of the interventions recommended by the National Health Service in many countries.

We can conclude that HEN is a safe, cost-effective treatment, which has become increasingly used in the last 20 years in Spain and in other western countries.

Acknowledgments

The authors extend their thanks to all the contributors to the NADYA registry and to B Braun, Spain for their technical support over these years.

References

1. Moreno JM, Shaffer J, Staun M, Hebuterne X, Bozzetti F, Pertkiewicz M et al. Survey on legislation and funding of home artificial nutrition in different European countries. *Clin Nutr* 2001; 20 (2): 117-23.
2. Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology* 1995; 109: 355-65.
3. Hebuterne X, Bozetti F, Moreno Villares JM, Pertkiewicz M, Shaffer J, Staun M et al. ESPEN-Home Artificial Nutrition Working Group. Home enteral nutrition in adults: A European multicentre survey. *Clin Nutr* 2003; 22: 261-6.
4. Gómez Candela C, De Cos AI, Vázquez C, Celaya S, García Luna PP, Pérez de la Cruz A et al. Grupo de trabajo nacional en nutrición artificial domiciliaria y ambulatoria. NADYA. *Nutr Hosp* 1995; 10 (5): 258-63.
5. Gómez Candela C, De Cos AI y grupo NADYA. Nutrición artificial domiciliaria. Informe anual 1994. Grupo NADYA. *Nutr Hosp* 1997; 12 (1): 20-27.
6. Gómez Candela C, De Cos AI, Iglesias C, Carbonell MD, Camarero E, Celador A, et al. Nutrición artificial domiciliaria. Informe anual 1995. Grupo NADYA-SENPE. *Nutr Hosp* 1998; 13 (3): 144-52.
7. Gómez Candela C, De Cos AI, Iglesias C, Carbonell MD, Camarero E, Carrera JA, et al. Nutrición artificial domiciliaria. Informe anual 1996. Grupo NADYA-SENPE. *Nutr Hosp* 1999; 14 (4): 145-52.
8. Gómez Candela C, De Cos AI, Iglesias C, Planas M, Castella M, García Luna PP et al. Nutrición enteral domiciliaria. Informe anual 1999. Grupo NADYA-SENPE. *Nutr Hosp* 2002; 17 (1): 28-33.
9. Planas M, Castellá M, García Luna PP, Chamorro J, Gómez Candela C, Carbonell MD et al. Nutrición enteral domiciliaria (NED): Registro nacional del año 2000. *Nutr Hosp* 2003; 18 (1): 24-8.
10. Planas M, Castellá M, García Luna PP, Parés RM, Chamorro J, Camarero E et al. Nutrición enteral domiciliaria (NED): registro nacional 2001. *Nutr Hosp* 2004; 19 (3): 145-9.
11. Planas M, Lecha M, García Luna PP, Chamorro J, Zamarrón I, Parés RM et al. Registro nacional de la nutrición enteral domiciliaria del año 2002. *Nutr Hosp* 2005; 20 (2): 254-8.
12. Planas M, Lecha M, García Luna PP, Parés RM, Chamorro J, Martí E et al. Grupo de trabajo NADYA-SENPE. Registro nacional de la nutrición enteral domiciliaria del año 2003. *Nutr Hosp* 2006; 21 (1): 71-4.
13. Cuerda C, Chicharro ML, Frías L, García Luna PP, Cardona D, Camarero E et al. Registro de la nutrición enteral domiciliaria en España en el año 2006 (Grupo NADYA-SENPE). *Nutr Hosp* 2008; 23 (2): 95-9.
14. Luengo LM, Chicharro ML, Cuerda C, García Luna PP, Rabassa A, Romero A et al. Registro de nutrición enteral domiciliaria en España en el año 2007. *Nutr Hosp* 2009; in press.
15. Moreno Villares JM, Cuerda C, Planas M, Gómez Candela C, León Sanz M, de Cos A et al. Trends in adult home parenteral nutrition in Spain. 1992-2003. *Nutr Hosp* 2006; 21 (5): 617-21.
16. Gómez Candela C, De Cos Blanco AI y grupo NADYA. Nutrición artificial domiciliaria y ambulatoria (NADYA). Nutrición enteral. *Nutr Hosp* 1995; X (5): 246-51.
17. Cuerda C, Parón L, Planas M, Gómez Candela C, Moreno JM y grupo NADYA-SENPE. Presentación del nuevo registro español de pacientes con nutrición artificial domiciliaria. *Nutr Hosp* 2007; 22 (4): 491-5.
18. Orden de 2 Junio de 1998, para la regulación de la nutrición enteral domiciliaria en el Sistema Nacional de Salud. Boletín Oficial del Estado, nº 139, (11-06-1998).
19. B.O.E. Nº 222, de 16 septiembre 2006. Real Decreto 1030/2006, de 15 de septiembre, por el que se establece la cartera de servicios comunes del Sistema Nacional de Salud y el procedimiento para su actualización.
20. Consejo Interterritorial del Sistema Nacional de Salud. Guía de práctica clínica de nutrición enteral domiciliaria. Madrid: Ministerio de Sanidad y Consumo, 1998.
21. Ministerio de Sanidad y Consumo. Guía de nutrición enteral domiciliaria en el Sistema Nacional de Salud. Madrid: Ministerio de Sanidad y Consumo, 2008.
22. De Luis DA, Aller R, Izaola O, Terroba MC, Cabezas G, Cuellar LA. Experience of 6 years with home enteral nutrition in an area of Spain. *European J Clin Nutr* 2006; 60: 553-7.
23. Pérez Méndez LF, García Mayor RV y grupo de trabajo de la Sociedad Gallega de Nutrición y Dietética. Situación actual de la nutrición enteral domiciliaria en Galicia. Estudio multicéntrico. *Nutr Hosp* 2001; 16 (6): 257-61.
24. Castaño A. Consumo de productos de nutrición enteral domiciliaria en la Comunidad Autónoma de Madrid. *Nutr Hosp* 2002; 17 (2): 107-11.
25. Castaño Escudero A, Pérez Gabarda ME. Nutrición enteral domiciliaria en la Comunidad de Madrid. *Nutr Hosp* 2004; 19 (2): 68-72.
26. Leyes P, Forga MT, Montserrat C, Coronas R. Nutrición enteral domiciliaria. Casuística del Hospital Clínico de Barcelona. *Nutr Hosp* 2001; 16 (5): 152-6.
27. Jones B, Micklewright A, Hirst A, Glencorse C, Baxter J, Khair J. Annual BANS Report 2008. Artificial Nutrition Support in the UK 2000-2007. www.bapen.org.uk/pdfs/bans_report/bans_report_08.pdf (Accessed 1/1/2009).

28. Van Gossum A. Home enteral nutrition. Epidemiology and legislation in Europe. Nestlé Nutrition Workshop Series Clinical & Performance Program 2005; 10: 59-71.
29. Pironi L, Candusso M, Biondo A, Bosco A, Castaldi P, Contaldo F et al. Prevalence of home artificial nutrition in Italy in 2005: a survey by the Italian Society for Parenteral and Enteral Nutrition (SINPE). *Clin Nutr* 2007; 26: 123-32.
30. Paccagnella A, Baruffi C, Pizzolato D, Favaro V, Marcon ML, Morello M et al. Home enteral nutrition in adults: a five-year (2001-2005) epidemiological analysis. *Clin Nutr* 2008; 27: 378-85.
31. Villar Taibo R, Martínez Olmos MA, Rodríguez Iglesias MJ, Fernández Rodríguez E, Prieto Tenreiro A. Home artificial nutrition in a sanitary area of Galicia (Spain): descriptive study and proposals for the future. *Nutr Hosp* 2008; 23 (5): 433-8.
32. DeLegge MH. Home enteral nutrition. Demographics and utilization in the United States. *Nestlé Nutrition Workshop Series Clinical & Performance Program* 2005; 10: 45-58.
33. DiBaise JK, Scolapio JS. Home parenteral and enteral nutrition. *Gastroenterol Clin N Am* 2007; 36: 123-44.
34. Roche V. Percutaneous endoscopic gastrostomy: Clinical care of PEG tubes in older adults. *Geriatrics* 2003; 58 (11): 22-9.
35. Valentini L, Schütz T, Allison S, Howard P, Pichard C, Lochs H. ESPEN Guidelines on Enteral Nutrition. *Clin Nutr* 2006; 25: 177-360.
36. Cervo FA, Bryan L, Farber S. To PEG or not to PEG. A review of evidence for placing feeding tubes in advanced dementia and the decision-making process. *Geriatrics* 2006; 61: 30-5.
37. Finucane TE, Christmas C, Leff BA. Tube feeding in dementia: How incentives undermine health care quality and patient safety. *J Am Med Dir Assoc* 2007; 8: 205-8.
38. Gómez Candela C, Cos Blanco A, García Luna PP, Pérez de la Cruz A, Luengo Pérez LM, Iglesias Rosado C, et al. Complicaciones de la nutrición enteral domiciliaria. Resultados de un estudio multicéntrico. *Nutr Hosp* 2003; 18 (3): 167-73.
39. Crosby J, Duerksen D. A retrospective survey of tube-related complications in patients receiving long-term home enteral nutrition. *Dig Dis Sci* 2005; 50 (9): 1712-7.
40. Iyer KR, Crawley TC. Complications of enteral access. *Gastrointest Endos Clin N Am* 2007; 17: 717-29.
41. Hébuterne X, Schneider SM. What are the goals of nutritional support? The example of home enteral nutrition. Nestlé Nutrition Workshop Series Clinical & Performance Program 2005; 10: 89-102.
42. Schneider SM, Raina C, Pugliese P, Pouget I, Rampal P, Hébuterne X. Outcome of patients treated with home enteral nutrition. *JPEN* 2001; 25: 203-9.
43. Sanders DS, Carter MJ, D'Silva J, James G, Bolton RP, Bardhan KD. Survival analysis in percutaneous endoscopic gastrostomy feeding: a worse outcome in patients with dementia. *Am J Gastroenterol* 2000; 95: 1472-5.
44. Elia M, Stratton RJ. A cost-utility analysis in patients receiving enteral tube feeding at home and in nursing homes. *Clin Nutr* 2008; 27: 416-23.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):354-356
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Casos clínicos

Severe hypocalcemia secondary to hypomagnesaemia, successfully treated by self-administered subcutaneous magnesium

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Abstract

We report the case of a patient with recurrent severe hypocalcemia, secondary to hypomagnesaemia, and prerenal renal failure, due to ileostomy losses after a colectomy, who needed several admissions to the hospital through more than one year. Finally, he was successfully treated by self-administered subcutaneous magnesium: he reached and maintained normal levels of serum calcium, magnesium and PTH, no more hospital admission were needed and he resumed a normal life.

(*Nutr Hosp*. 2009;24:354-356)

Key words: *Hypocalcemia. Hipomagnesaemia. Self administration. Magnesium.*

HIPOCALCEMIA SEVERA, SECUNDARIA A HIPOMAGNESEMIA, TRATA DA CON ÉXITO MEDIANTE AUTO-ADMINISTRACIÓN SUBCUTÁNEA DE MAGNESIO

Resumen

Se trata de un paciente con hipocalcemia severa recurrente, secundaria a hipomagensemia, y fracaso renal agudo prerrenal secundario a perdidas digestivas a través de una ileostomía, tras una colectomía. Por este motivo necesitó varios ingresos hospitalarios a lo largo de más de un año. Finalmente fue tratado con éxito mediante auto-administración subcutánea de magnesio. Con este tratamiento mantuvo niveles nornmales de calcio, magnesio y PTH, no requirió más ingresos hospitalarios y recuperó una vida normal.

(*Nutr Hosp*. 2009;24:354-356)

Palabras clave: *Hipocalcemia. Hipomagnesemia. Auto-administración. Magnesio.*

Introduction

Hypocalcemia is an important clinical entity which causes abnormal neurological sensations and neuromuscular hyperexcitability.[1] One of the causes of hypocalcemia is hypoparathyroidism, which can be secondary to hypo- magnesaemia.[1] Magnesium deficiency due to gastrointestinal disease is usually treated with oral supplements. Some patients who do not need parenteral nutrition suffer chronic and recurrent fluid and electrolyte depletion despite oral supplementation,[1] so that they need parenteral magnesium supplementation. We report the case of a patient with recurrent severe hypocalcemia secondary to hypomagnesaemia and prerenal renal failure successfully treated by self-administered subcutaneous magnesium.

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Recibido: 2-IX-2008.
Aceptado: 4-XII-2008.

Case report

A 71-year-old man, former smoker, with past medical history of hypertension, hyperlipidemia and surgery for an abdominal aortic aneurysm, was diagnosed of rectum carcinoma and treated by chemotherapy and radiotherapy prior to an anterior resection of rectum with colorectal anastomosis and protection ileostomy. After surgery he was admitted to the hospital twice because of prerenal acute renal failure secondary to ileostomy losses, and successfully treated by intravenous fluid replacement.

Nine months after rectum surgery, a right and transverse colectomy was performed because the patient had colonic polyps, and a postsurgical ischemic cholitis led to a left colectomy and a terminal ileostomy. He had a prerenal acute renal insufficiency secondary to high ileostomy losses after this second surgery.

Table I
Clinical and biochemical evolution of the patient before subcutaneous magnesium treatment

Weeks after anterior resection of rectum	4	40	52	55	59
Clinical events	Acute renal insufficiency	Total colectomy and terminal ileostomy. Acute renal insufficiency	Admission. Vomits and fever. Seizures. Admission on ICU	Admission. Fever, tremor, asthenia	Admission. Asthenia. Tremor. Subcutaneous magnesium was initiated during this admission
Total serum calcium (mmol/l) Normal range: 2.15-2.55			1.55	1.68	1.58
Ionized calcium (mmol/l) Normal range: 1.15-1.29			0.63	0.8	0.91
Serum magnesium (mmol/l) Normal range: 0.66-1.07			0.42	0.08	0.21
PTH (pg/ml) Normal range: 10-65			26	44	57
Creatinine (µmol/l) Normal range: 62-106	504	636	256	230	194

Three months after the colonic resection he was again admitted to the hospital due to vomiting and fever. Five days after admission he was transferred to the Intensive Care Unit because he had seizures secondary to severe hypocalcemia and acute renal failure. He was discharged on treatment with loperamide, oral calcium and calcitriol, but had to be readmited one week later because he had severe hypocalcemia secondary to hypomagnesaemia and prerenal acute renal failure. He was treated with intravenous infusion of fluids, calcium and magnesium and he was discharged. Oral supplements of magnesium, codeine and octreotide were added to the previous treatment. He came back two weeks later (five months after colectomy): he reported tremor and intense discomfort and was admitted again because of severe hypocalcemia, hypomagnesaemia and acute renal insufficiency. The first day he was treated with intravenous infusion of saline solution, calcium chloride and magnesium sulfate, and the second day was transferred to subcutaneous administration of saline solution with magnesium sulfate (12 mmol of magnesium sulfate in 1,000 ml of saline solution during 12 hours) via a butterfly needle. The patient and his wife were instructed about self-administered subcutaneous fluid infusion and he was discharged three days after admission with the following daily treatment: oral calcium gluconate, calcitriol, codeine and a self-administered subcutaneous infusion of 500 ml of saline solution with 6 mEq of magnesium sulfate during 6 hours per day. He was advised to increase saline administration to 1,000 ml per day if diuresis diminished or ileostomy losses increased.

After this admission patient has had normal levels of serum calcium, magnesium and PTH. Hospital admission has not been needed and renal function has remained stable. The patient, whose daily activities had been very limited since colectomy, has resumed a normal life.

Table I summarises clinical and biochemical evolution before subcutaneous magnesium treatment. Table II summarises biochemical evolution after this treatment.

Discussion

Hypocalcemia can be caused by hypoparathyroidism, PTH resistance, vitamin D deficiency, medications, congenital causes, malignancy, and some severe diseases. Hypomagnesaemia causes both hypoparathyroidism and PTH Resistance.[1] Causes of hypomagnesaemia include gastrointestinal losses (including acute or chronic diarrhoea, malabsortion and steatorrhea, or short bowel syndrome), renal losses (including diuretics, volume expansion, alcoholism, hypercalcemia, nephrotoxins and loop of Henle or distal tubule dysfunction)[3] and intracellular redistribution (including refeeding syndrome).

Symptoms of hypocalcemia include abnormal neurological sensations and neuromuscular excitability and central nervous system manifestation like seizures, mental status changes and irritability.[1] Hypomagnesaemia is usually asymptomatic but it can produce neuromuscular irritability, hypokalemia and cardiac arrhythmia.[4] Seizures secondary to hypomagnesaemia in gastrointestinal diseases have been previously reported.[5]

Our patient's hypocalcemia was secondary to hypoparathyroidism, and maybe PTH resistance, secondary

Table II
Biochemical evolution of the patient after subcutaneous magnesium treatment

Days after discharge	2	5	9	16	35	68	98	137
Total serum calcium (mmol/l) Normal range: 2.15-2.55	2.15	2.37	2.35	2.42	2.36	2.45	2.48	2.45
Serum magnesium (mmol/l) Normal range: 0.66-1.07	0.71	0.76	0.76	0.67	0.76	0.71	0.67	0.71
PTH (pg/ml) Normal range: 10-65	111	70	49	49	34	28	31	40
Creatinine (µmol/l) Normal range: 62-106	133	124	124	133	115	115	106	124

to hypomagnesaemia, since his PTH level was low or inappropriately normal for his hypocalcemia, and not high, as it is expected in non-PTH related hypocalcemia.

Our patient's high-output ileostomy was responsible for the repeated episodes of dehydration and acute renal failure, in a similar way as it happens in chronic diarrhoea. We think it was also responsible for hypomagnesaemia, that was worsened by the absence of the colon, an organ with magnesium-absorbing capacity.[4] The remarkable improvement with subcutaneous administration of a dose of magnesium close to the 10 mMol usually absorbed per day through the gastrointestinal tract[4] reinforce this etiology, since this treatment would not have corrected a hypomagnesemia originated from renal magnesium wasting.

Hypocalcemia was resistant to treatment with oral calcium and calcitriol (consistently with diagnosis of hypocalcemia secondary to hypomagnesaemia) and oral supplements of magnesium were not effective. Self-administered subcutaneous fluid and magnesium infusion was an effective alternative, avoided new admissions and improved the quality of life of our patient.

Previous reports of self-administered subcutaneous $MgSO_4$ infusion are scarce and authors emphasize the usefulness and easiness of this treatment.[2] Our experience supports that it is a practical and safe method of managing hydroelectrolytic deficiencies in patients who do not respond to oral treatment.

Conclusions

Hypomagnesaemia secondary to gastrointestinal diseases can produce hypoparathyroidism and severe hypocalcemia with seizures and other complications. Self-administered subcutaneous fluid and magnesium infusion is an effective alternative in patients with malabsortion or increased losses who do not respond to oral treatment and do not need total parenteral nutrition.

References

1. Guise TA, Mundy GR. Clinical review 69: Evaluation of hypocalcemia in children and adults. *J Clin Endocrinol Metab* 1995; 80: 1473-1478.
2. Martínez-Riquelme A, Rawlings J, Morley S, Kendall J, Hosking D, Allison S. Self-administered subcutaneous fluid infusion at home in the management of fluid depletion and hypomagnesaemia in gastro-intestinal disease. *Clin Nutr* 2005; 24: 158-163.
3. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol* 1999; 10: 1616-1622.
4. Topfs JM, Murray PT. Hypomagnesemia and hypermagnesemia. *Rev Endocr Metab Disord* 2003; 4: 195-206.
5. Fernández-Rodríguez E, Camarero-González E. Paciente con enfermedad de Crohn y convulsiones por hipomagnesemia. *Nutr Hosp* 2007; 22: 720-722.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):357-360
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Casos clínicos

¿Es la edad un factor limitante en la distribución de recursos? Nutrición parenteral domiciliaria en el paciente anciano

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Resumen

Un grupo de bioeticistas defiende la idea de que la edad del paciente debe ser un criterio mayor en la distribución de recursos sanitarios limitados. Mientras que las principales indicaciones de Nutrición Enteral Domiciliaria ocurren frecuentemente en edades avanzadas (secuelas de accidente cerebrovascular, demencia, cáncer de cabeza y cuello, etc.) se carece de datos sobre el uso y las características de la nutrición parenteral domiciliaria (NPD) en el paciente anciano. Señalamos las peculiaridades del empleo de esta técnica en un paciente > 75 años con NPD prolongada y la justificación de su empleo con independencia de la edad.

Se trató de un varón de 77 años que sufrió una isquemia intestinal masiva con resección de yeyuno, ileon, colon ascendente y mitad de transverso y anastomosis yeyuno cólica. Tras una estancia hospitalaria de dos meses se envió a su domicilio con NPD. Su cuidadora habitual era su esposa de 72 años de edad, afecta de una enfermedad de Parkinson incipiente. La NPD se mantuvo durante 11 años, siendo suspendida a raíz del deterioro clínico. Durante este periodo tuvo 5 infecciones asociadas a catéter (tasa de infección: 1,3 episodios por cada 1.000 días de NPD); 1 salida accidental de catéter. Precisó recambiar el catéter en 4 ocasiones (vida media del catéter: 788 días). Fue hospitalizado en cuatro ocasiones por complicaciones de la técnica. La situación funcional al inicio de la NPD era de vida activa independiente y pasó a vida sedentaria pero autónoma al final de la misma.

***Conclusiones:* La tasa de complicaciones en NPD en el paciente comentado no fue distinta de lo que ocurre en otros grupos de edad. La técnica no supuso una carga de trabajo excesiva para el cuidador habitual, aunque se tratara también de una persona anciana. La edad en sí no debe constituir un factor limitante a la hora de proporcionar soporte nutricional a domicilio.**

(*Nutr Hosp*. 2009;24:357-360)

Palabras clave: *Nutrición parenteral. Anciano. Complicaciones. Ética.*

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Recibido: 2-XI-2008.
Aceptado: 9-XI-2009.

IS OLDER AGE A LIMITING FACTOR WHEN CONSIDERING HEALTH RESOURCES? THE CASE OF HOME PARENTERAL NUTRITION

Abstract

Some bioethicists consider older age as a limiting factor for receiving special medical care. Older adults comprise the majority of home enteral nutrition patients (neoplams of the head, neck, and upper gastrointestinal tract neuromuscular swallowing disorders, dementia, etc) On the contrary, there are very few data on Home Parenteral Nutrition (HPN) in the elderly. We report these of a 75 years old man affected from a severe short bowel syndrome due to mesenteric thrombosis. After a hospital stay of two months he was sent home on HPN. His current caregiver was her wife, a 72 year old woman suffering from incipient Parkinson's disease.

HPN lasted for 11 years and was stopped because of clinical deterioration. During this time he presented 5 catheter-related infections (1.3 episodes/1,000 days). 5 catheters were used (average length 788 days). He was hospitalized four times because of HPN complications. Functional status was maintained along almost all the length of HPN.

***Conclusions:* The rate of complications in this patient was similar to other groups of age receiving HPN. The technique was not burdensome for the family. Older age cannot be consider, by itself a limiting factor when receiving long term nutritional support.**

(*Nutr Hosp*. 2009;24:357-360)

Key words: *Parenteral nutrition. Elderly. Complications. Ethics.*

Proponer una nutrición artificial a domicilio en una persona anciana y/o dependiente puede constituir a la vez un problema médico y ético. Un grupo de bioeticistas, encabezados por D. Callahan *(Setting limits: medical goals in an aging society"),* defiende la idea de que la edad del paciente debe ser uno de los criterios mayores que influya en la distribución de recursos sanitarios limitados. Frente a esta postura otros argumentan que cuando se toman decisiones clínicas sobre las personas mayores debe calibrarse la edad, pero también muchos otros factores. La edad debe ser un elemento, pero no un factor determinante.

Mientras que las principales indicaciones de Nutrición Enteral Domiciliaria ocurren frecuentemente en edades avanzadas (secuelas de accidente cerebrovascular, demencia, cáncer de cabeza y cuello, etc.) (fig. 1)[1] son muchos menores los datos sobre el uso y las características de la nutrición parenteral domiciliaria (NPD) en el paciente anciano. En los últimos datos publicados del registro NADYA-SENPE, < 5% de los pacientes con NPD eran mayores de 74 años (fig. 2)[2].

Señalamos las peculiaridades del empleo de esta técnica en un paciente > 75 años con NPD prolongada a causa de un fracaso intestinal de causa benigna y la justificación de su empleo con independencia de la edad.

Caso clínico

Se trató de un varón de 77 años con antecedentes de fibrilación auricular crónica que sufrió una isquemia intestinal masiva con resección de yeyuno, ileon, colon ascendente y mitad de transverso realizándose una anastomosis yeyuno-cólica. Tras una estancia hospitalaria de dos meses se envío a su domicilio con NPD siete días a la semana, infundiéndose a lo largo de 10 horas. Su cuidadora habitual era su esposa de 72 años de edad, afecta de una enfermedad de Parkinson incipiente. Además disponía de una familia cercana muy involucrada.

La NPD se mantuvo durante 11 años, siendo suspendida a raíz del deterioro clínico causado por una neumonía de la comunidad. La duración total fue de 3.940 días. Durante este periodo tuvo 5 infecciones asociadas a catéter (tasa de infección: 1,3 episodios por cada 1.000 días de NPD) y 1 salida accidental de catéter. Precisó recambiar el catéter en 4 ocasiones (vida media del catéter: 788 días). Presentó desde los dos años del inicio de la NPD una esteatosis hepática leve, no progresiva. Fue hospitalizado en cuatro ocasiones por complicaciones de la técnica. La situación funcional al inicio de la NPD era de vida activa independiente y pasó a vida sedentaria pero autónoma al final de la misma. Durante los primeros ocho años de NPD se desplazaba una o dos veces al año para disfrutar de unos días de vacaciones en la playa.

Discusión

El escenario que se presenta en el mundo occidental, con un marcado envejecimiento de la población, obliga a una reflexión ética sobre la atención al anciano (fig. 3). El anciano tiene un patrón de pérdida de funciones propio, que le hace muy distinto de otros pacientes con enfermedades terminales.

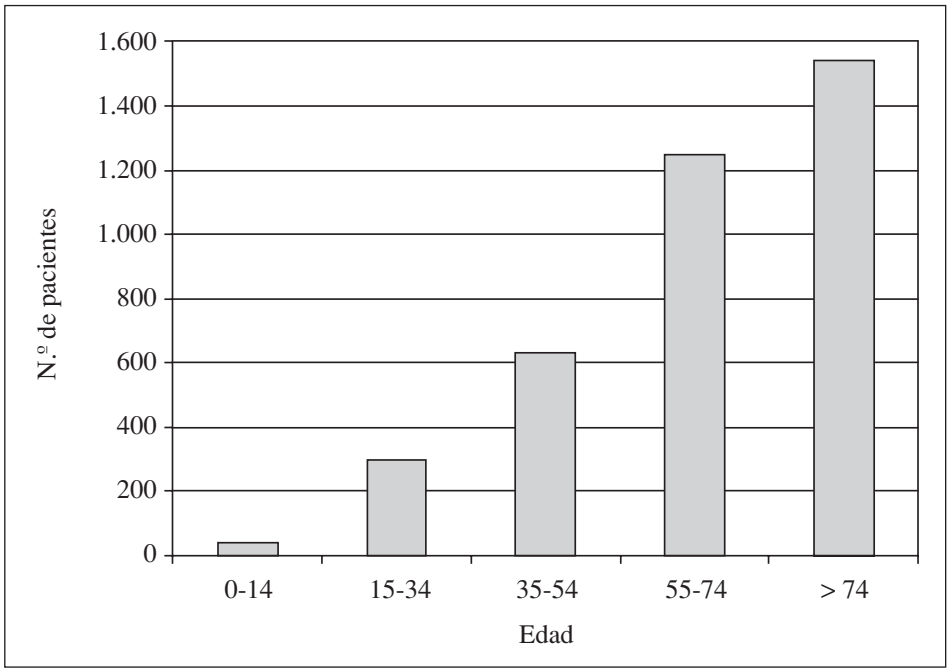

Fig. 1.—Distribución por edades de los pacientes con NED en el año 2003 (datos de registro NADYA-SENPE. Publicado en Nutr Hosp 2006; 21: 71-4).

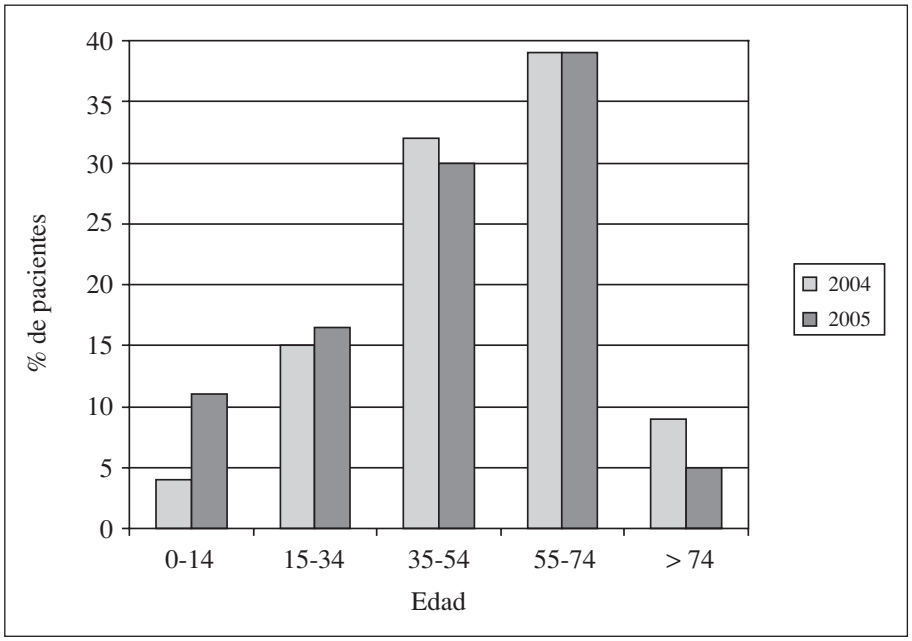

Fig. 2.—Distribución por edades de los pacientes con NPD en los años 2004 y 2005 (datos de registro NADYA-SENPE. Publicado en Nutr Hosp 2007; 22: 307-12).

Indudablemente la edad es un criterio importante a la hora de asignar recursos de salud, sobre todo en función del tipo de intervención[3]. Ante una situación de recursos limitados y demanda creciente, ¿qué parámetros deben tenerse en cuenta? ¿Cómo conseguir una atención médica equitativa, es decir, que toda la población reciba el mismo cuidado para la misma necesidad?[4]

Uno de los posibles escenarios clínicos en esta edad es el de una resección intestinal amplia secundaria a un problema vascular, como ocurrió en nuestro caso[5]. Como en otras situaciones médicas deben considerarse de forma clara los riesgos y beneficios de la técnica. Pueden servir como guía las siguientes preguntas: 1) ¿va a ser bien tolerada?, 2) ¿va a mejorar o a mantener el estado nutricional del paciente?, 3) ¿va a mejorar su calidad de vida? Y 4) ¿va a mejorar el pronóstico o la supervivencia del paciente?[6]. La respuesta a algunas de estas preguntas se obtiene de forma sencilla y puede cuantificarse (por ejemplo la tolerancia o la repercusión sobre el estado nutricional), mientras que las consideraciones sobre la calidad de vida son más complejas. La calidad de vida puede entenderse como una vida digna donde la persona se siente plenamente realizada, toda vez que sus objetivos y expectativas se van cumpliendo. Si bien, cada sujeto experimenta esa realidad de un modo subjetivo, dependiendo de su situación, de

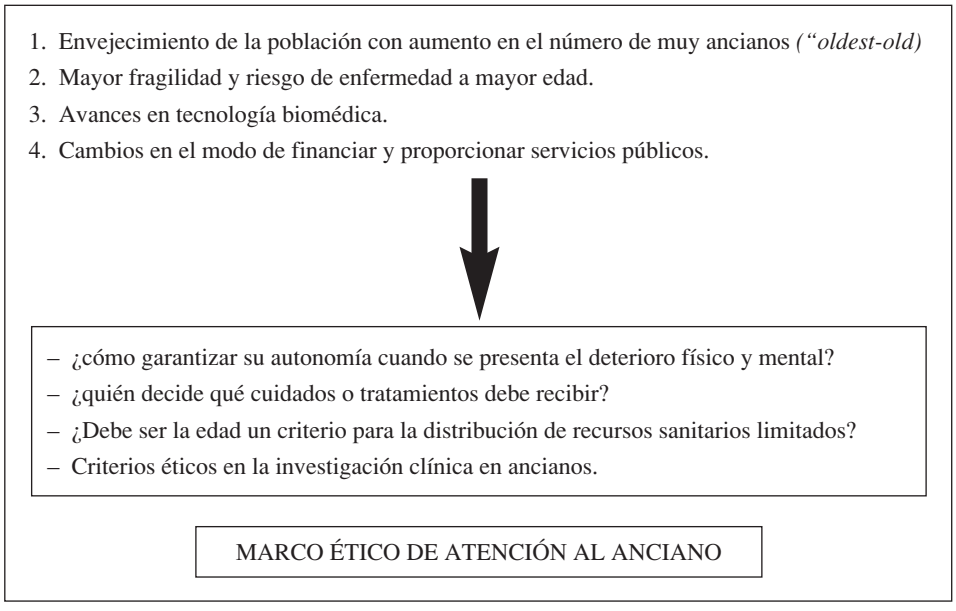

Fig. 3.—Escenario actual.

su época y de su cultura. A priori podemos suponer que cuando el anciano adopta una actitud dinámica ante la vida, emprendedora y optimista, tiene muchas probabilidades de vivir su última etapa con dignidad y calidad[7]. Este planteamiento también es cierto en el caso de la enfermedad.

Si lo consideramos bajo el prisma de los principios bióeticos, además de contar con el consentimiento del paciente y de la valoración del riesgo-beneficio, atentaría contra la justicia si se privara de un tratamiento demostrado eficaz a un paciente sólo si se considerara su edad elevada. Como también lo sería si la discriminación lo fuera por razón de raza, ideas o medio social. Si nos atenemos a la condición vital de nuestro paciente, se cumple el hecho observado por otros especialistas de que las personas mayores involucrados en actividades de grupo, con relaciones afectivas significativas tienden a vivir más.

Sólo si el seguimiento se realiza con unos estándares de calidad es posible que el número de complicaciones sea bajo y que la satisfacción del paciente y sus cuidadores sea elevada[8].

En un marco referencial más amplio podemos asegurar que el organismo humano experimenta el proceso de envejecimiento: los tejidos pierden flexibilidad, los órganos reducen la calidad de sus funciones y el ritmo vital de las células se atenúa. Pero el envejecimiento en sí no es una enfermedad. Existen incluso algunas funciones que no sólo no se pierden con la edad, sino que se enriquecen cualitativamente siempre y cuando encuentren un ambiente propicio[9]. Estas consideraciones deben tenerse en cuenta en el caso de que el anciano enferme. La edad como único condicionante no es aceptable.

Conclusiones

La tasa de complicaciones en NPD en el paciente comentado no fue distinta de lo que ocurre en otros grupos de edad. La técnica no supuso una carga de trabajo excesiva para el cuidador habitual, aunque se tratara también de una persona anciana. La edad en sí no debe constituir un factor limitante a la hora de proporcionar soporte nutricional a domicilio. La NPD debe considerarse en el paciente anciano dentro del modelo de "fragilidad".

Referencias

1. Puiggros C, Chicharro ML, Gómez-Candela C, Virgili N, Cuerda C, Gómez Enterría P, Ordóñez J y cols. Registro español de Nutrición Parenteral Domiciliaria 2006; *Nutr Hosp* 2008; 23: 6-11.
2. Planas M, Lecha M, García Luna PP, Parés RM, Chamorro J, Martí E, et al. Registro nacional de la nutrición enteral domiciliaria del año 2003. *Nutr Hosp* 2006; 21: 71-4.
3. Rodríguez E, Pinto JL. The social value of health programes: is age a relevant factor? *Health Economics* 2000; 9: 611-21.
4. La Rosa Salas V, Tricas Sauras S. Equity in health care. *Cuad Bioét* 2008; 19: 355-68.
5. Howard L, Malone M. Clinical outcome of geriatric patients in the United Status receiving home parenteral and enteral nutrition. *Am J Clin Nutr* 1997; 66: 1364-70.
6. Hébuterne X. La lettre du président : faut-il envisager la nutrition artificielle à domicile chez un malade dépendant? *Nutr Clin Métabol* 2006; 20: 119-20.
7. Cuenca Molina A. Calidad de vida en la tercera edad. *Cuad Bioet* 2008; 19: 271-91.
8. Silver HJ, Wellman NS, Arnold DJ, Livingstone AS, Byers PM. Older adults receiving home enteral nutrition: enteral regimen, provider involvement, and health care outcomes. *J Parent Ent Nutr* 2004; 28: 92-8.
9. Moragas R. Gerontología Social. Envejecimiento y calidad de vida. Herder. Barcelona, 1998, p. 34.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):361-363
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Casos clínicos

Síndrome del histiocito azul marino en relación a nutrición parenteral domiciliaria

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Resumen

Presentamos un caso de un varón de 55 años con Enfermedad de Crohn de larga evolución con mala respuesta al tratamiento médico y múltiples fístulas al que se le inició nutrición parenteral domiciliaria (NPD) tras su última resección intestinal. Presentaba hepatopatía crónica no filiada y pancitopenia leve. Tras 9 meses de soporte nutricional parenteral se produce un empeoramiento de la función hepática y la pancitopenia. Se realizó biopsia de médula ósea que mostró histiocitos azul marino. La evolución fue tórpida falleciendo a consecuencia de un fallo multiorgánico.

(*Nutr Hosp*. 2009;24:361-363)

Palabras clave: *Histiocito azul marino. Nutrición parenteral. Hepatopatía. Pancitopenia. Lípidos.*

SEA-BLUE HISTIOCYTE SYNDROME ASSOCIATED WITH HOME PARENTERAL NUTRITION

Abstract

A case of a 55 years-old male with long-term Crohn´s disease without response to medical treatment and many intestinal fistula is presented. After the last bowel resection, home parenteral nutrition was started. He presented chronic hepatopathy and pancytopaenia. After 9 months of home parenteral nutrition hepatic function and pancytopaenia began to deteriorate. Bone marrow examination revealed an infiltrate of sea-blue histiocytes. He made insatisfactory progress and died due to a multiorganic failure.

(*Nutr Hosp*. 2009;24:361-363)

Key words: *Sea-blue histyocite. Parenteral nutrition. Hepatopathy. Pancytopenia. Lipids.*

Introducción

El histiocito azul marino fue descrito por primera vez en 1947 por Möschlin. Se trata de macrófagos que contienen gránulos de fosfolípidos que se tiñen de azul marino con la tinción de May-Giemsa. Estas células han sido descritas en diferentes trastornos del metabolismo lipídico como el Síndrome de Niemann-Pick o el Síndrome de Gaucher, así como en varias patologías hematológicas. En 1970, Silverstein[1] describió el Síndrome del Histiocito Azul Marino (SHAM) que cursa con hepatoesplenomegalia y/o pancitopenia por acumulación de histiocitos azules en médula ósea y/o hígado. La etiología es desconocida. Aunque habitualmente su curso es benigno puede evolucionar desfavorablemente hacia una cirrosis. Hay muy pocos casos descritos en la literatura[2-4] y algunos de ellos asociados a nutrición parenteral domiciliaria[5-6].

Caso clínico

Presentamos el caso un de un varón de 55 años con enfermedad de Crohn de larga evolución con múltiples fístulas y resecciones intestinales por mala respuesta al tratamiento médico. Tras la última intervención quirúrgica se realizó exclusión intestinal con gastrostomía de descarga y se inició nutrición parenteral. Estaba diagnosticado de hepatopatía crónica no filiada con trombosis portal, varices esofágicas y pancitopenia leve. El paciente presentaba peso al alta de 50 kg, talla de 170 cm e IMC de17,3 kg/m^2. Al alta se inició tratamiento con Nutrición Parenteral Domiciliaria (NPD) diaria compuesta por 35 kcal/kg/día (14g de nitrógeno, 225 g de glucosa, 50 g de lípidos MCT/LCT).

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Recibido: 17-XII-2008.
Aceptado: 2-II-2009.

Tabla I
Evolución de los parámetros bioquímicos desde el inicio de la NPD

	Plaquetas	*Bilirrubina*	*AST/ALT*	*Triglicéridos*	*Albúmina*
Comienzo	64.000	2,6	46/56	65	2,9
3º mes	106.000	1,6	35/28	83	3,3
6º mes*	61.000	6,8	58/46	132	2,7
9º mes	30.000	22,7	170/147	240	1,9

Durante los primeros meses la evolución fue favorable con mejoría del estado general, de la pancitopenia, parámetros nutricionales y función hepática. A los 6 meses se produjo un deterioro de la función hepática con colestasis y empeoramiento de la pancitopenia; por lo que se disminuyó el aporte de grasas, oligoelementos y vitaminas liposolubles (tabla I). Posteriormente empeoró el estado general del paciente con fiebre e ictericia intensa precisando ingreso hospitalario. En la analítica del ingreso presentaba importante aumento de bilirrubina, coagulopatía, trombocitopenia severa y disminución de los niveles de albúmina con ferritina en valores normales.

La ecografía abdominal mostró hepatopatía crónica sin datos de obstrucción de la vía biliar, trombosis portal y esplenomegalia. La biopsia hepática presentaba una arquitectura mantenida, espacios porta con infiltrados inflamatorios y éstasis biliar de predominio centrolobulillar con fenómenos de necrosis hepatocitaria. En la punción de médula ósea se observó celularidad medular conservada con acúmulo de histiocitos con material lipofuccínico PAS+ (histiocitos azul marino) que constituían al menos el 20% de la celularidad total, sin hemofagocitosis (figs. 1 y 2).

Se le administraron 3 dosis de anti-TNFα como tratamiento de su enfermedad de base además de s-adenosilmetionina, con eliminación total de las grasas en la nutrición parenteral. La evolución fue desfavorable presentando insuficiencia hepatocelular, encefalopatía hepática, hemorragia digestiva y neumonía nosocomial, evolucionando a fallo multiorgánico y muerte.

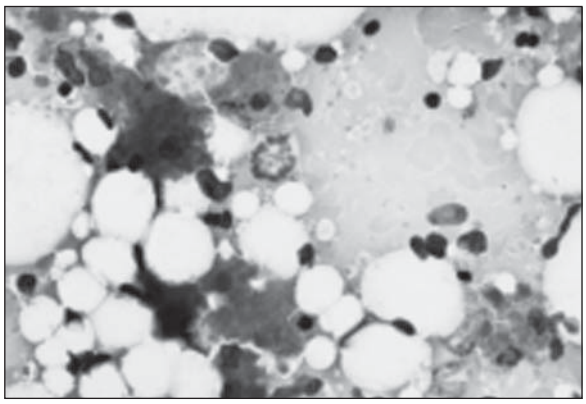

Fig. 1.—Imagen al microscopio óptico de la médula ósea (tinción de PAS).

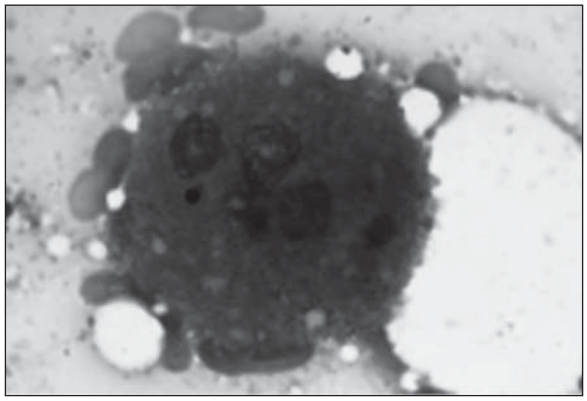

Fig. 2.—Imagen al microscopio óptico a mayor aumento con histiocito azul marino.

Discusión

La presencia de histiocitos azul marino en médula ósea se ha descrito en múltiples patologías. Esta denominación se debe a que los gránulos del interior del histiocito se tiñen de azul marino con la tinción de May-Giemsa. Estos gránulos corresponden a acúmulos lipídicos que se ponen de manifiesto con la tinción de PAS. La acumulación de lípidos de dichas células se debe a la incapacidad de los lisosomas de digerir el exceso de grasa. Puede deberse a la presencia de alteraciones enzimáticas como en el Síndrome de Gaucher o el Síndrome de Niemann-Pick[7], o al aumento de la destrucción de membranas celulares como ocurre en la Leucemia Mieloide Crónica.

El SHAM además de presentar estas células se caracteriza por la presencia de hepatoesplenomegalia. En estos pacientes no se ha descrito ninguna alteración enzimática. Aunque la fisiopatología es desconocida, la hepatoesplenomegalia producida por acúmulo patológico de estos histiocitos podría alterar la función hepática y producir una situación de hiperesplenismo. La pancitopenia podría ser explicada por una combinación de hiperesplenismo y probable hematopoyesis defectuosa por síntesis anormal de los fosfolípidos de las membranas celulares.

Existe cierta controversia en la literatura entre el Síndrome de Activación Macrofágica (MAS) y el SHAM. Para algunos autores este último sería un subtipo del MAS. La principal diferencia entre ambos es la presencia de hemofagocitosis e hiperferritinemia en el MAS, que no está presente en el SHAM[8-12].

Aunque la hepatopatía es una complicación frecuente en los pacientes con NPD[13-15], sin embargo se han descrito pocos casos de SHAM. La mayoría son casos aislados[5-6]. Bignone y cols.[16] realizaron biopsias de médula ósea en 7 pacientes tratados con NPD (3 de ellos con emulsiones lipídicas con triglicéridos de

cadena larga y media LCT/MCT, el resto con LCT) con leves alteraciones clínicas y analíticas, encontrando la presencia de histiocitos azul marino en todos los casos. A la vista de este hallazgo es posible que la presencia de estas células sea más prevalente que la encontrada en la práctica clínica y que preceda a las manifestaciones clínicas del SHAM. La asociación de este síndrome con la NPD podría deberse al aumento de los niveles de lípidos en sangre que podría sobrecargar su aclaramiento por las células fagocitarias. Algunos autores han descrito una mejoría en la evolución de estos pacientes al disminuir el aporte de grasas en la nutrición parenteral[17]. Dado que en los casos descritos se utilizaron emulsiones lipídicas con contenido mayoritario en LCT o mezclas MCT/LCT se desconoce el efecto que pudieran tener las nuevas emulsiones lipídicas (con ácido oleico, omega-3) en la aparición de este síndrome.

Referencias

1. Silverstein MN, Ellefson RD, Ahern EJ. The syndrome of the sea-blue histiocyte. *N Engl J Med* 1970; 282: 1-4.
2. Hirayama Y, Kohda K, Andoh M, Matsumoto S, Nakazawa O, Nobuoka A y cols. Syndrome of the Sea-Blue Histiocyte. *Intern Med* 1996; 35: 419-21.
3. Tachibana F, Hakozaki H, Takahashi K, Kojima M, Enomoto S, Wada J. Syndrome of the sea-blue histiocyte – The first case in Japan and review of the literature. *Acta Pathol Jpn* 1979; 29: 73-97.
4. Kaur A, Sudarsanam A, Pulimood RB. Syndrome of the sea-blue histiocyte (a report of 2 cases). *Indian J Pathol Microbiol* 1984; 27: 111-5.
5. Meiklejohn DJ, Baden H, Greaves M. Sea-blue histiocytosis and pancitopaenia associated with chronic total parenteral nutrition administration. *Clin Lab Haem* 1997; 19: 219-21.
6. Bignone C, Tourneau ALE, Vahedi K, Rio B, Messing B, Molina T y cols. Sea-blue histiocyte in bone marrow secondary to total parenteral nutrition. *Leuk Lymphoma* 1998; 28: 523-9.
7. Suzuki O, Abe M. Secondary Sea-Blue Histiocytosis derived from Niemann-Pick disease. *J Clin Exp Hematopathol* 2007; 47:19-21.
8. Pérez-Jaffe L, Furth E, Minda J, Unger L, Lawton T. Massive macrophage lipid accumulation presenting as hepatoesplenomegaly and lymphadenopathy associated with long-term parenteral nutrition therapy for short bowel syndrome. *Hum Pathol* 1998; 29: 651-5.
9. Pradalier A, Teillet F, Molitor JL, Drappier JC. Macrophage activation syndrome, hemophagocytic syndrome. *Pathol Biol* 2004; 52: 407-14.
10. Ravelli A. Macrophage activation syndrome. *Curr Opin Rheumatol* 2002; 14: 548-52.
11. Grom A. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr Opin Rheumatol* 2003; 15: 587-90.
12. Koduri PR, Caradang G, DeMarais P, Patel AR. Hyperferritinemia in reactive hemophagocytic syndrome. Report of four adult cases. *Am J Hematol* 1995; 49: 247-9.
13. Guglielmi FW, Moran Penco JM, Gentile A y cols. Hepatobiliary complications of long-term home parenteral nutrition. *Clin Nutr* 2001; 20 (Supl. 2): 51-5.
14. Shaffer JL. Hepatic complications of parenteral nutrition. *Clin Nutr* 1995; 14: 59-64.
15. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsion in cholestasis associated with long-term parenteral nutrition in children. *JPEN J Parenter Enteral Nutr* 2000; 24: 345-50.
16. Bignone C, Tourneau ALE, Messing B, Rio B, Giraud V, Molina T y cols. Sea-blue histiocyte syndrome in bone marrow secondary to total parenteral nutrition including fat-emulsion sources: a clinicopathologic study of seven cases. *Br J Haematol* 1996; 95: 258-62.
17. Goulet O, Girot R, Maier-Redelsperger M, Bougle D, Virelizier JL, Ricour C. Hematologic disorders following prolonged use of intravenous fat emulsion in children. *JPEN J Parenter Enteral Nutr* 1986; 10: 284-8.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):364-367
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Cartas científicas

Efecto del calcio sobre la pérdida de peso

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Estimado Director:

En estudios de observación y en ensayos aleatorios de corta duración, se han descrito asociaciones negativas entre el consumo de calcio y el índice de masa corporal (IMC), el porcentaje de grasa y la circunferencia de cintura. El propósito de este estudio fue analizar los efectos a largo plazo del calcio sobre el peso corporal. Se realizó una búsqueda de MEDLINE para identificar los ensayos aleatorios controlados (RCT), publicados en inglés o español, con productos lácteos o suplementación con calcio, de enero del 2000 a marzo del 2008 con una intervención igual o mayor a 48 semanas. Para la búsqueda se utilizaron los descriptores "weight loss" con otras palabras claves: "dairy products", "obesity" y ¨calcium supplementation¨. Se excluyeron estudios realizados en personas con diabetes mellitus, otras condiciones médicas o que estuvieran bajo tratamiento farmacológico. Se analizaron las siguientes características: el diseño de estudio, número de participantes, porcentaje de seguimiento, edad, sexo, IMC, tiempo de intervención, fuente de calcio, reducción de peso, diferencia entre grupos y nivel de significancia. Se encontraron cuatro estudios[1-4]. Todos los estudios tuvieron un diseño paralelo, la fuente de calcio fueron los productos lácteos y la retención al final de cada estudio osciló de 32% a 81%. Las fuentes alimentarias de calcio fueron a partir de leche baja en grasa y yogurt. En los tres estudios donde se observó una reducción significativa de peso se prescribió una dieta con restricción calórica de 500 kcalorias. En dos de ellos aumentaron la actividad física (tabla I).

En todos los estudios analizados en esta revisión no se observaron diferencias en la pérdida de peso entre los grupos control y el experimental. Estos resultados son similares a las conclusiones obtenidas en revisiones recientes[5]. Se han descrito diversos mecanismos mediante los cuales el calcio podría tener un efecto sobre el peso o la composición corporal. Algunos autores sugieren que la disminución de la ingesta de calcio dietética puede resultar en un aumento de los niveles de calcio intracelular, el cual interviene en la modulación de los depósitos de triglicéridos, podría aumentar lipogénesis, e inhibir la lipólisis y la termogénesis. También se ha propuesto que el calcio dietético podría inhibir la absorción de grasas en el tracto gastrointestinal y aumentar la pérdida de ácidos grasos por las heces. Sin embargo, los estudios de observación han demostrado resultados inconsistentes.

De acuerdo a los estudios aleatorios registrados en MEDLINE en el período estudiado, se puede concluir que en los ensayos bien diseñados y a largo plazo no hay evidencias del efecto benéfico del consumo de calcio y lácteos sobre el peso y la composición corporal, lo que es consistente con estudios prospectivos a largo plazo. Se sugiere estudios aleatorios controlados de más largo plazo, con adecuado control de consumo calórico, de macronutrientes y de actividad física, con la estimación del poder estadístico y que permitan valorar el efecto del calcio sobre la pérdida de peso.

Referencias

1. Bowen J, Noakes M, Clifton MP. A high dairy protein, high calcium diet minimizes bone turnover in overweight adults during weight loss. *J Nut* 2004; 134: 568-573.
2. Harvey-Berino J, Casey Gold B, Lauber R, Starinski A. The impact of calcium and dairy product consumption on weight loss. *Obes Res* 2005; 13: 1720-1726.
3. Thompson WG., Rostad Holdman N, Janzow DJ, Slezak JM., Morris KL, Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. *Obes Res* 2005; 13: 1344-1353.
4. Eagan M S, Lyle RM, Gunther CW, Peacock M, Teegarden D. Effect of 1 year dairy product intervention on fat mass in young women: 6 month follow-up. *Obesity* 2006; 14: 2242-2248.
5. Trowman R, Dumville JC, Hahn S, Torgerson DJ. A systematic review of the effects of calcium supplementation on body weight. *Br J Nutr* 2006; 95: 1033-1038.

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Recibido: 22-IX-2008.
Aceptado: 20-I-2009.

Tabla I
Estudios sobre el efecto del calcio sobre la pérdida de peso

Autor, año	*Diseño RCT*	*N inicial*	*% seguimiento*	*Edad*	*Sexo (N)*	*IMC (kg/m²)*	*Tiempo*	*Fuente de calcio*	*Calcio mg/día*	*Reducción de peso (peso y grasa en kg, CC en cm)*	*Diferencia entre grupos*	*Comentarios*
Bowen y cols., 2004[1]	Paralelo	156	32%	20 a 65	M F	27 a 40	16 meses	Productos lácteos	A: 2.371 ± 45 B: 509 ± 24	A: -9 ± 0,6 kg[o] B: -9,3 ± 0,7 kg	NS	Hubo restricción calórica de 500 kcal/día. No se reportó poder estadístico. Los resultados reportados son durante el período de restricción calórica.
Harvey y cols., 2005[2]	Paralelo	54	81%	18 a 60	M (4) F	25 a 34,9	12 meses	Productos lácteos	A: 400 a 500	-9,6 ± 6,5 kg[o]	NS	Aumentaron la actividad física y disminuyeron la ingesta calórica (500 kcal.). Poder estadístico 9%.
										-9,0 ± 3,8 kg grasa[o]		
									B: 1.200 a 1.400	-10,8 ± 5,9 kg[o]		
										-10,1 ± 3,6 kg grasa		
										-2,75 ± 0,73 kg grasa[¥]		
										-0,58 ± 1,04 cm[1]		
								Yogurt	B: 1.110	-6,63 ± 0,6 kg[+]		
										-4,43 ± 0,47 kg grasa[¥]		
										-3,99 ± 0,48 cm[1]		
									B: 1.000	B: -11,02 kg[o]		
									B: 500	B: -7,8 ± 0,6 kg[2]		
Thompson y cols., 2005[3]	Paralelo	118	45%	25 a 70	F	A: 35 B: 35 C: 35	48 semanas	Productos lácteos	A: 800 B: 1.400 C: 1.450	A: -11 ± 6,9 kg[3] B: -11,2 ± 5,9 kg[3] C: -11,9 ± 7,8 kg[3]	NS	Restricción calórica de 500 kcal. Realizaban por lo menos 30 min/d 4 veces/sem de actividad física. Poder estadístico de 80%. Los resultados reportados fueron de los participantes que se mantuvieron más del 75% de la dieta y actividad física.
Eagan y cols., 2006[4]	Paralelo	154	33%	20,1	F	A: 22 B: 23 C: 22	18 meses	Productos lácteos	A: < 800	0,4 ± 1,7 kg[o]	NS	Se valoró actividad física. No se reportó poder estadístico.
										-0,39 ± 1,99 kg grasa[3]		
									B: 1.000 a 1.100	0,1 ± 6,7 kg[o]		
										-0,32 ± 4,94 kg grasa[3]		
									C: 1.300 a 1.400	0,3 ± 3,0 kg[o]		
										-0,43 ± 2,8 kg grasa[3]		
								Leche baja en grasa	B: 1.188	B: -3,76 ± 2,25 kg[2]		

F: Femenino; M: Masculino; [o] No disponible; [1] $p < 0,001$; [2] $p < 0,05$; [3] estadísticamente no significativo; [+] $p < 0,01$; [¥] $p < 0,005$; CC: circunferencia de cintura; IMC: índice de masa corporal.

Cartas científicas

Reliability and validity of self-reported weight and height in Belgium

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Recently some nutrition surveys rely on self-reported weights and heights for the estimation of body-mass-index' (BMI) based nutritional status, particularly when modern online data collection methods are applied.[1] It is still under debate whether such procedures are valid or reliable. On the one hand, self-reported height and weight are considered as feasible, useful measures in large scale studies,[2] while on the other hand, overestimation of self-reported height and underestimation of self-reported weight have been documented as a sources of individual bias independently of gender.[3]

The only way to evaluate performance of self-reported anthropometric information is by comparing those values against actual measures. Hence, a small-scale study was carried out in Belgium between March and April 2008 to assess the reliability and validity of such values. The convenience sample included 71 participants: 37 women (mean age 38 y; SD17) and 34 men (mean age 36 y; SD16). Each respondent had to fill a short socio-demographic questionnaire and register their weights and heights. Three weeks later, they were asked to repeat the exercise (test-retest reliability). University students weighed and measured each respondent according to standard procedures[4] to obtain true values as reference.

Normality of data was assessed with the Kolmogorov-Smirnov test. Differences between self-reported and actual measures of height and weight were assessed using Student's T-test for normally distributed variables. The non-parametric Wilcoxon Signed Ranks Test was used to compare non-normally distributed variables. All tests were performed with a significance level of 0.05.

At an aggregated level all variables were normally distributed, with exception of measured height (P = 0.024). When evaluated by respondent's gender, all women's variables presented normal distribution, including estimated BMI. Men's self reported heights and weights were normally distributed; however,

Table I

*Correlations and differences between self-reported and measured height and weights in a sample of Belgium adults**

Variables	*All Pearson's Correlation r*	*Difference between means*	*P-value of the difference*	*Women Pearson's Correlation r*	*Difference between means*	*P-value of the difference*	*Men Pearson's Correlation r*	*Difference between means*	*P-value of the difference*
Weight 1-Weight 2 (in kg)	0,996	-0,04	0,773	0,990	-0,16	0,394	0,996	0,10	0,494
Weight 1-Weight measured (in kg)	0,736	-2,76	0,226	0,978	-1,68	<0,001	0,592	-3,92	<0,001#
Weight 2-Weight measured (in kg)	0,731	-2,72	0,067	0,984	-1,52	<0,001	0,580	-4,02	<0,001#
Height 1-Height 2 (in cm)	0,997	0,10	0,073	0,989	0,11	0,422	0,997	0,09	0,324
Height1-Height measured (in cm)	0,421	1,75	0,044	0,986	0,30	0,148	0,151	3,32	0,143#
Height 2-Height measured (in cm)	0,422	1,65	0,089	0,984	0,19	0,213	0,149	3,24	0,142#
BMI 1-BMI 2 in kg/m^2	0,990	-0,04	0,466	0,987	-0,08	0,274	0,992	0,01	0,842#
BMI 1-BMI measured in kg/m^2	0,114	-4,16	0,257	0,969	-0,70	<0,001	0,046	-7,93	0,155#
BMI 2-BMI measured in kg/m^2	0,102	-4,12	0,262	0,981	-0,61	<0,001	0,030	-7,94	0,278#

* Student's T-test unless indicated otherwise.
# Wilcoxon Signed Ranks Test .

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Recibido: 27-I-2009.
Aceptado: 11-II-2009.

actual measures and corresponding calculated BMI were not.

Table I shows correlations and differences between self-reported and measured heights and weights in this sample. No statistical differences were found between self-reported weights and actual measures of weight. The difference between the first self-reported height and the actual measure was significant for the whole group. No statistical differences could be observed between first and second self-reported values and the consequent BMI estimate. For women all correlations between self-reported and measured values were significant, suggesting that females are more reliable in self assessment of height and weight. The opposite holds for males.

The paradoxical message of this study is that in this sample of Belgian adults, self reporting of heights and weights is reliable (respondents provided the same values twice) but not valid (inaccurate values) despite high correlations with actual measurements. As expected, overweight levels estimated on the basis of self-reported heights and weights would be underestimated.[5] This limitation should be addressed when reporting results based on self-reported anthropometric data.

References

1. Matthys C, Pynaert I, De Keyzer W, De Henauw S. Validity and reproducibility of an adolescent web-based food frequency questionnaire. *J Am Diet Assoc* 2007; 107 (4): 605-10.
2. Goodman E, Strauss RS. Self-reported height and weight and the definition of obesity in epidemiological studies. *J Adolesc Health* 2003; 33 (3): 140-141.
3. Danubio ME, Miranda G, Vinciguerra MG, Vecchi E, Rufo F. Comparison of self-reported and measured height and weight: Implications for obesity research among young adults. *Econ Hum Biol* 2008: 6 (1): 181.
4. WHO (World Health Organization) Physical Status: the use and interpretation of anthropometry. World Health Organization Technical Report Series, Editor. 1995: Geneva, pp. 375-411.
5. Gorber SC, Tremblay M, Moher D, Gorber B. Diagnostic in obesity comorbidities - A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007: 8(4): 307-326.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):368-370
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Cartas al director

Valoración de la circunferencia de la pantorrilla como indicador de riesgo de desnutrición en personas mayores

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Sr. Director:

En relación con el artículo "Valoración de la circunferencia de la pantorrilla como indicador de riesgo de desnutrición en personas mayores"[1], llama la atención una sucesión de afirmaciones:

1º) El objetivo de la investigación no define si se va a comprobar la validez del Mini Nutritional Assessment Test con su posterior ratificación por los hallazgos en las mediciones de la circunferencia de la pantorrilla.

2º) No se aclara si el observador de las mediciones fue el mismo, para descartar los errores sistemáticos que pudieran existir.

3º) La confiabilidad de las mediciones no fue comprobada al no usarse la prueba estadística del coeficiente alfa de Cronbach[2], necesaria para asegurar la consistencia de las mismas.

4º) Los pacientes registrados eran aquellos que, *"en su mayoría"*, acudían a la oficina de Farmacia, sin aclarar si las encuestas realizadas eran realmente de pacientes ambulatorios o internados sin movilización (probable sesgo de selección).

5º) No surgen los criterios y grados de riesgo de desnutrición y su correlación con los parámetros normales y la razón para determinar un valor de corte de 31 cm de circunferencia de pantorrilla con el fin de establecer resultados de normalidad.

6º) En varios párrafos de los resultados y discusión se hace referencia a la *gran mayoría de personas,* sin aclarar su real frecuencia.

La aclaración de estos interrogantes, surgidos mediante una lectura crítica del material aquí presentado, permitirá una mejor comprensión de una investigación que a todas luces es muy necesaria y útil. La sola existencia de resultados con significación estadística no debe hacer creer que lo sean de importancia y significación clínica[3] y por eso es tan meritorio este tipo de pesquisas para hallar, con datos precisos y claros, un valor indirecto de riesgo del estado nutricional que se sumara a otras mediciones antropométricas ya probadas.

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Recibido: 17-IV-2009.
Aceptado: 24-IV-2009.

Referencias

1. Cuervo M, Ansorena D, García A, González Martínez MA, Astiasaran I, Martínez J.A. Valoración de la circunferencia de la pantorrilla como indicador de riesgo de desnutrición en personas mayores. *Nutr Hosp* 2009; 24: 63-67.
2. Hernández Sampieri R, Fernández Collado C, Baptista Lucio P. Metodología de la investigación. Mc Graw Hill, México, 2000, p. 242.
3- Arribalzaga EB. Delimitación de un área de investigación. Análisis de los conocimientos existentes y elaboración de nuevas cuestiones. En Esper RJ y Machado RA. La investigación en medicina. Prensa Médica Argentina, Buenos Aires, 2008, pp. 140-154.

Réplica de los autores

Sr. Director:

Valoramos muy positivamente sus comentarios y el interés mostrado en nuestro artículo "Valoración de la circunferencia de la pantorrilla como indicador de riesgo de desnutrición en personas mayores" de Cuervo y cols.[1]

En relación a los comentarios señalados en su carta:

1º) El objetivo concreto de la investigación no era definir la validez del cuestionario Mini Nutritional Assessment (MNA) en nuestra población, sino estimar el impacto de la circunferencia de la pantorrilla como indicador de una posible situación de desnutrición en personas mayores. De hecho, estudios complementarios relacionados con la interpretación del MNA en nuestra población han sido previamente publicados[2].

2º) En la recogida de datos y medidas, participaron 3.251 farmacéuticos, tal y como se detalla en el apartado "Selección y formación de encuestadores" de la sección "Sujetos y métodos" del artículo. Para evitar errores sistemáticos, se preparó un manual de medida que fue

explicado y entregado a cada uno de los farmacéuticos participantes. Asimismo, se realizaron 50 reuniones en los Colegios Oficiales de Farmacéuticos (COF's) provinciales y se impartió una sesión por videoconferencia conjunta desde el Consejo General de COF's que fue recibida en todos los COF's provinciales.

3º) La comprobación de la confiabilidad de las mediciones a través del coeficiente alfa de Cronbach, resultó en un valor de 0,731 lo que aseguraría la consistencia de las mediciones.

4º) La distribución de personas encuestadas (n = 22.007) fue: 79,4% en oficina de farmacia, 3,5% en centro asistencia y el 17,0% en otros centros sociales como club de jubilados y centros cívicos. Aunque no puede descartarse un sesgo de selección, las personas que acuden a una oficina de farmacia en general, pertenecen a estratos muy diversos de la población y no imponen las restricciones de población institucionalizada y hospitalizada.

5º) El MNA es un cuestionario que puede hacerse en dos pasos: una primera versión reducida, que consta de 6 preguntas con un puntuación máxima de 14. Si el resultado es 12, 13 ó 14 puntos, se descarta el riesgo de desnutrición y no es necesario continuar con el cuestionario. Si el resultado es 11 o inferior, no se descarta el riesgo de desnutrición y es necesario completar el cuestionario hasta el final. Si el resultado final presenta menos de 17 puntos, sobre la puntuación máxima (30 puntos) indica que existe una situación de desnutrición por lo que el paciente debe ser derivado al médico para una exploración clínica más completa. Si el resultado se encuentra entre 17 y 23,5 puntos (ambos incluidos) se sugiere una situación de riesgo de desnutrición y por encima de 23,5 puntos es indicativo de ausencia de desnutrición. Parte de esta interpretación, puede encontrarse en el apartado "Descripción del Mini Nutritional Assessment (MNA)" de la sección "Sujetos y métodos" del artículo.

Los puntos de corte aplicados para valorar la circunferencia de la pantorrilla (31 cm) como indicador de desnutrición, fueron los propuestos por los investigadores que desarrollaron y validaron el MNA[3].

6º) La afirmación correspondiente a "la gran mayoría" que aparece la inicio del tercer párrafo de la sección "Resultados y discusión" hace referencia a los valores que se muestran en la figura 1 del artículo.

Reiterando nuestro agradecimiento por los comentarios y el tiempo dedicado a la lectura crítica de este artículo, coincidimos con el Dr. Arribalzaga en que no todo lo estadísticamente significativo tiene relevancia clínica.

Referencias

1. Cuervo M, Ansorena D, García A, González Martínez MA, Astiasaran I, Martínez JA. Valoración de la circunferencia de la pantorrilla como indicador de riesgo de desnutrición en personas mayores. *Nutr Hosp* 2009; 24: 63-67.
2. Cuervo M, García A, Ansorena D, Sánchez-Villegas A, Martínez-González M, Astiasarán I, Martínez JA. Nutritional assessment interpretation on 22 007 Spanish community-dwelling elders through the Mini Nutritional Assessment test. *Public Health Nutr* 2009; 12 (1): 82-90.
3- Vellas B, Guigoz Y, Garry PJ y cols. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 1999; 15 (2): 116-22.

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Cartas al director

Under nutrition - a major health problem in Europe

Desnutrición, un problema sanitario de gran magnitud en Europa

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[1]Professor of Surgery. Nutrition and Metabolism. Karolinska Institutet. Stockholm. Sweden. Chairman ESPEN. Co-Chairman, European Nutrition for Health Alliance ENHA. [2]General Secretary. ENHA. Sweden.

El presidente de ESPEN (Sociedad Europea de Nutricion Parenteral y Enteral), Dr. Olle Ljungqvist, se dirige a los miembros de SENPE para informar sobre las acciones que, inspiradas por ESPEN, se van a emprender desde la presidencia de la Comunidad Europea al objeto de combatir la malnutrición en los hospitales y entre los ancianos, un problema que no por pasar desapercibido deja de ser de gran magnitud. El tema será motivo de un encuentro de ministros de Sanidad de la Comunidad Europea durante el mes de Junio de 2009. Desde la presidencia de ESPEN se propone un plan de

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accion que consta de seis puntos que la SENPE hace suyos.

Dear Editor,
Dear members of SENPE,

Under nutrition, poor nutritional status or as it is commonly phrased malnutrition is Europe's hidden major health problem. This week, the EU presidency of the Czech Republic invites all health ministries and world experts to a two-day conference aimed at tackling this major problem.

In Spain and in Europe, the world's richest region, disease related malnutrition is a major health problem for society and for health care. This fact has recently been identified in the EU. In 2003 the Council of Europe published the "Resolution on food and nutritional care in hospitals" and is recently followed by a similar resolution for care homes. Last autumn, the European Parliament decided that malnutrition in hospitals and other care situations was to be a central feature in the coming five year 'Together for Health' strategy for the entire European Union. The present Czech EU Presidency now responds to this call by inviting the Health Ministries of all EU countries to meet with the European expertise on nutrition to find ways to jointly tackle this major health problem in Prague later this week. In the presidency to follow, in Sweden, an upcoming conference on the elderly should be an important follow up since malnutrition is particularly common, with 10-20% of this age group affected by malnutrition.

The tip of the ice berg

Malnutrition does not show up in the streets in Europe. Instead malnutrition is a hidden health problem, residing at home or in care homes. At least 25% of all patients admitted to hospitals are malnourished or at risk for malnutrition. Overall, five per cent of the population in Europe is estimated to be at risk for malnutrition. Substantially higher figures have repeatedly been reported from every kind of care situation, in particular in the elderly where at least 10% have malnutrition or are at risk of developing malnutrition. Very recent figures from Sweden show that 15% of the individuals' ages 75-80+ living at home are at risk for malnutrition. Malnutrition associated with disease is associated with markedly higher risks for complications/comorbidity, poor quality of life, increased need for care both as out patients and in hospitals and care institutions. Malnourished patients have a higher mortality compared to well nourished patients. In the UK shows 3 million citizens suffer from malnutrition. The situation is similar all over Europe with regard to malnutrition as shown by studies performed in 70 000 patients and individuals in care homes performed by the European Society for Clinical Nutrition and Metabolism (ESPEN). Hence, the UK situation then transforms to at least 33 million Europeans suffering from malnutrition. The cost for disease related malnutrition in the UK was estimated to about 15 billion euro. Again on a European scale this transforms to at least 170 billion euro annually.

A call for joint action

Numerous studies have shown that nutritional treatment to the malnourished patient improves outcomes, reduces the cost for care and improves quality of life. In the UK the cost spent on nutritional treatment is only about 2,5% of the cost for malnutrition. Other studies show that the average net savings from oral nutritional supplements in hospital costs is about 1,000 euros per patient, mainly related to shorter length of stay an less need for care.

The main obstacles to improving nutritional care lies in the lack of awareness for the problem among the general public, but also among decision makers and even care providers. To battle this major problem a global effort is needed involving all stakeholders. ESPEN, in association with their respective national society for clinical nutrition and metabolism alongside the European Nutrition for Health Alliance has initiated a major effort to improve nutritional care. The targets for improvements in the care of the malnourished includes:

- Public awareness and education
- Guideline development and implementation.
- Training in nutritional care.
- Mandatory screening for malnutrition.
- National nutritional care plans for nutrition.
- Research on malnutrition.

With the upcoming conference in Prague organised by the EU presidency, we are ready to launch this pan European movement to minimize the impact of malnutrition in Europe. We invite all health ministers and their ministries to join us and place our experiences and expertise at their disposal to tackle this major health problem.

Nutrición Hospitalaria

Nutr Hosp. 2009;24(3):371-373
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Crítica de libros

El aceite de oliva, alma del Mediterráneo

Olive oil, soul of the Mediterranean region

J. M.ª Mataix Verdú y F. J. Barbancho Cisneros. 437 páginas. Editorial: Instituto de Estudio Gienenses-Diputación de Jaén.
Año de edición: 2008. ISBN: 978-84-96047-59-4.

Este libro sobre el aceite de oliva, primorosamente editado por la Diputación Provincial de Jaén, permite al recientemente fallecido profesor Mataix y al pediatra Francisco Barbancho realizar un riguroso y ameno recorrido sobre el aceite, en lo sagrado y lo profano, de sus propiedades nutricionales y usos industriales. Un recorrido que también pasa por los desafíos. Del temprano comercio del aceite español dan muestra las ánforas del monte Testaccio en Roma; de la pérdida de mercados y valor añadido, son testigos los cónsules españoles ya desde comienzos del XIX; de las propiedades nutricionales y terapéuticas se da fe desde los médicos grecorromanos hasta nuestros días. Calidad, comercialización, desarrollo sostenible y salud, prioridades en la cooperación actual entre el tejido empresarial y administraciones públicas.

En cada una de las páginas de la publicación aparece destilada la pasión por el aceite que los autores transmiten con un rigor y sensibilidad capaces de convencer al experto y cautivar al novel. Su conocimiento del tema no sólo se ciñe a las disciplinas en las que se desempeñan como profesionales en medicina y nutrición, sino que nos ofrece una visión multidisciplinar que mezcla el cultivo, la historia, la antropología y, como no podía ser de otra manera, la perspectiva desde el bienestar y la salud. Abundan entre el texto mapas e ilustraciones históricas que van desde un grabado de D. Quijote aliviando las heridas de Sancho hasta imágenes de los comentarios al Apocalipsis del Beato de Liébana (siglo XI). Aunque sólo sea para hojear las estampas, es un libro que merece la pena ser tenido entre las manos.

Jesús M. Culebras

Actualizaciones en el metabolismo y la nutrición de órganos y sistemas

Update in metabolism and nutrition of organs and systems

M. Planas Vilá. 528 páginas. Editorial: Aula Médica Ediciones.
Año de edición: 2009. ISBN: 978-84-7885-486-8.

Desde hace al menos cuatro años, la SENPE organiza, con el Patrocinio de Nutricia, un curso durante los congresos anuales de SENPE que es acreditado por la Secretaría Técnica de la Comisión de Formación continuada de las profesiones sanitarias de la Comunidad de Madrid. Estos cursos se han caracterizado por una gran aceptación y valoración por parte del público asistente.

Cada año los distintos trabajos presentados en el curso han sido motivo de un monográfico extraordinario de la revista "Nutrición Hospitalaria". En esta ocasión los autores han decidido reunir todo lo tratado en cursos anteriores; pero no se trata de una mera recopilación: cada uno de los autores ha realizado una revisión y puesta al día de sus distintos capítulos con la finalidad de actualizar posibles novedades más recientes. Este libro contiene, por tanto, los conceptos mas actuales sobre los diversos aparatos y sistemas que de alguna manera se interrelacionan con la nutrición clínica.

El libro está repartido en 4 partes: la primera trata de la relaciones entre el músculo y la nutrición clínica; la segunda entre el intestino y la nutrición clínica; la tercera entre el hígado, vías biliares, páncreas y nutrición clínica; la última las relaciones entre el sistema nervioso y la nutrición clínica. En un total de más de 500 páginas los casi 80 autores consiguen que este libro se constituya en un manual de utilización frecuente para la práctica diaria.

Jesús M. Culebras

De la pregunta de investigación a la ecuación de búsqueda bibliográfica: los descriptores en las ciencias de la nutrición

From the question in research to the bibliographic search equation. Descriptors in nutritional sciences

J. Sanz-Valero y C. Wanden-Berghe. 67 páginas. Editorial: Ene Ediciones, S. L.
Año de edición: 2009. ISBN: 978-84-85395-76-7.

Esta nueva obra de Javier Sanz Valero y Carmina Wanden-Berghe concluye la trilogía que, bajo el Patrocinio del Laboratorio Abbott, cierra el primer ciclo de actuación del grupo de trabajo CDC-NUT de la SENPE. Se trata de un manual evidentemente práctico en el que los autores nos permiten familiarizarnos en la búsqueda de la bibliografía científica, las bases de datos bibliográficas informatizadas, en la estructura jerárquica con los descriptores versus las palabras clave, con los filtros y en especial con los filtros temáticos en nutrición. Al final se incluye un anexo con los principales descriptores relacionados con la alimentación y la nutrición. La lectura atenta y la utilización de este manual, al igual que los anteriores, de esta trilogía, permiten una mayor profesionalidad a la hora de escribir artículos científicos de toda índole. Ajustarse estrictamente a la normativa de referencias bibliográficas: palabras clave, citaciones, etc… permite que la recuperación de los artículos se realice de la mejor manera, con lo cual se benefician de una mayor difusión que es, en definitiva, el fin último de nuestras publicaciones.

Todos los libros de esta trilogía son accesibles en Internet a través de la página web de SENPE (www.senpe.com).

Gonzalo Martín Peña

Índice glucémico - clasificación fisiológica de los hidratos de carbono de la dieta

Glycemic index - physiological classification of dietary carbohydrates

T. M. S. Wolever. 287 páginas. Editorial: Acribia, S. A.
Año de edición: 2009. ISBN: 978-84-200-1104-2.

Se trata de otro libro de la colección Nutrición Ciencia y Tecnología de los Alimentos, de Editorial Acribia S.A..

Con tapas rústicas y en nueve capítulos, nos ofrece este manual una introducción histórica, la determinación del índice glucémico de los alimentos con consideraciones metodológicas, la respuesta de insulina de los alimentos con hidratos de carbono y la evaluación crítica del índice insulilémico; los mecanismos por los cuales los hidratos de carbono diferentes dan lugar a distintas respuestas glucémicas; el índice glucémico y su aplicación en la mezcla de comidas; la medición del índice glucémico en la dieta; el índice glucémico en la salud y en la enfermedad y, finalmente, el índice glucémico versus carga glucémica.

El término "índice glucémico", apareció en la bibliografía por primera vez en 1981. Se aplicó inicialmente al tratamiento de la diabetes y hubo un gran debate y grandes diferencias de opinión acerca de su papel a este respecto. Durante quince años se cuestionó la utilidad del índice glucémico. Sin embargo, en los últimos diez años ha surgido un interés público y científico por este índice porque ha llegado a ser evidente que la salud y el desarrollo humano están influidos por el IG en diversas vías. De particular interés ha sido el papel del IG en el manejo del peso corporal y es cada vez mayor el número de libros dedicados a dietas que hacen referencia a él.

Jesús M. Culebras

Manual de dietas simplificado
A simplified manual of diets

A. K. Maher. 206 páginas. Editorial: Acribia, S. A.
Año de edición: 2007. ISBN: 978-84-200-1106-6.

Es un manual de dietas de diversas naturaleza. En 12 capítulos y un amplio apéndice se describen las directrices para la preparación de dietas; dietas habituales; dietas con consistencia alterada, dietas líquidas y sus modificaciones, dietas para el control de peso, dietas en la diabetes, dietas con restricción en grasas, dietas con restricción en sodio, dietas en la enfermedad renal y hepática, dietas con modificación sin fibra, otras dietas modificadas. El último capítulo trata sobre la asistencia en el comedor y las necesidades especiales. Finaliza el libro con una serie de otros 12 apéndices informativos de dietas recomendadas de referencia, de clasificaciones y de contenidos de diversos elementos en los alimentos.

Jesús M. Culebras

Nutrition in kidney disease
Nutrición en la enfermedad renal

L. D. Byham-Gray, J. D. Burrowes, G. M. Chertow. 621 páginas. Editorial: Humana Press.
Año de edición: 2008. ISBN: 978-1-58829-781-5.

En este libro, Nutrición en la Enfermedad Renal, los autores proporcionan una perspectiva amplia sobre la ciencia emergente de la nutrición en la enfermedad renal. Este libro importante ha sido escrito por un grupo de dietistas y médicos dedicados al campo específico de la enfermedad renal y la nutrición clínica, que han dedicado sus carreras al cuidado de pacientes con esta patología. Al final de cada capítulo aparecen casos clínicos que ilustran el tema tratado.

La primera parte se refiere a la función renal en la salud y la enfermedad. Las partes II y III proporcionan una información profunda sobre la prevención de las enfermedades comunes asociadas con la enfermedad renal crónica; las opciones de tratamiento habituales basadas en la evidencia científica más reciente y en su manejo. La parte IV describe los problemas nutricionales y las necesidades especiales. La parte V habla de otros problemas nutritivos en la enfermedad renal tales como: la nutrición complementaria, la nutrición alternativa, los aspectos culturales que afectan al seguimiento de las dietas y los resultados de la investigación reciente.

El libro Nutrición en la Enfermedad Renal es una herramienta muy útil para los médicos relacionados con la nutrición y la nefrología. Está distribuido en 25 capítulos con un total de 621 páginas, tapas duras y una edición muy cuidada.

Jesús M. Culebras

Nutrición y bienestar - aspectos culturales, genéticos y metabólicos
Nutrition and fitness - cultural, genetic and metabolic aspects

A. P. Simopoulos. 259 páginas. Editorial: Karger.
Año de edición: 2008. ISBN: 978-3-8055-8530-9.

Es un volumen que contiene una selección de artículos de trabajos presentados en la Conferencia de Nutrición y Bienestar, celebrada en Shangai en Noviembre de 2006, bajo el Patrocinio del Congreso Mundial sobre Nutrición, Bienestar y Salud.

En el libro se definen los conceptos: nutrición, bienestar, salud positiva, desde la Antigüedad hasta el momento actual. Posteriormente hay una serie de artículos centrados en la importancia de los ácidos grasos Omega 3 y Omega 6 en la salud y en la enfermedad. En otros capítulos se trata sobre los riesgos genéticos de enfermedad cardiovascular, del impacto del genotipo APO-E sobre la salud, la nutrición y el bienestar, la nutrición en la prevención de la enfermedad crónica, la conexión entre el ejercicio y la obesidad. Hay otros artículos sobre los factores de riesgo en el cáncer intestinal. También se habla de las dietas mediterráneas como una fuente global para protección de la salud. Finalmente se tratan algunos aspectos políticos de la nutrición.

El libro es de interés para genetistas, nutricionistas y dietistas, fisiólogos del ejercicio, antropólogos, pediatras, internistas, médicos generales y en definitiva para todos los que tienen alguna relación con el deporte.

Jesús M. Culebras